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JOSEPH LEE LILIENTHAL, JR.

Joseph Lilienthal, Associate Editor of this JOURNAL, died suddenly on Nov. 19, 1955, from coronary occlusion. Thus abruptly ended, at the early age of 44, a brilliant career in medicine.

A graduate of Yale (1933) and of the Johns Hopkins Medical School (1937), he was best known in scientific circles for his basic studies of neuromuscular function and of respiratory physiology. His achievements led to academic advancement and a broadening of his fields of interest. He was Associate Professor of Medicine and Professor of Environmental Medicine, respectively, in the Schools of Medicine and of Hygiene and Public Health of the Johns Hopkins University; a member of the Association of American Physicians, the American Society for Clinical Investigation, the American Clinical and Climatological Association; and consultant to many Federal agencies dealing with health.

His aid in the Editorship of this JOURNAL was invaluable. His perceptive, analytic mind and his editorial comments, sometimes refreshingly pungent, were of great value to the contributors of manuscripts and to his associates on the editorial staff.

To those who knew him well, and especially to those who worked for or with him, the loss of his professional abilities, his companionship, his clear thinking, his energy, and his stimulus to others will be keenly missed.

His closest associates will most often recall his gentleness, thoughtfulness, cheerfulness, sympathetic understanding, sparkling conversation and wit, and his affectionate friendship.

We express not only our personal sense of sorrow, but also the general regret that so promising a scientific career should have been so tragically ended before greater fulfillment.

JOSEPH EARLE MOORE
DAVID SEEGAL

Original Communications

HERITABLE DISORDERS OF CONNECTIVE TISSUE

IV. The Ehlers-Danlos Syndrome

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HISTORICAL NOTE

NONE of the hereditary disorders of connective tissue, except possibly osteogenesis imperfecta, has as ancient a history as does the Ehlers-Danlos syndrome. The first definitive case* of this syndrome seems to have been described in 1682[94] by Job van Meekeren, a surgeon of Amsterdam. In Fig. 1 is presented van Meekeren's illustration of the "extraordinary dilatability of the skin" in a 23-year-old Spaniard who could pull the right pectoral skin to the left ear, the skin under the chin up over the head like a beard, and the skin of the knee area out about one-half yard. On being released, the skin retracted promptly to fit snugly over the underlying structures. This phenomenon was limited to the skin of the right side of the body.

Various dermatologists, including Kopp[44] and Williams[102] published scattered references to this condition, which was usually observed as a curiosity in "India rubber men" of side shows. Kopp's report in 1888 is particularly noteworthy since he described the condition in father and son. Gould and Pyle[33] published the photograph made in Budapest in 1888 of an exhibitionist named Felix Wehrle, "who besides having the power to stretch his skin could readily bend his fingers backward and forward." Du Mesnil[23] in 1890, Williams[102] in 1892, working in Unna's laboratory in Hamburg, and Unna[93] himself in 1894 reported on histologic studies. In general, these authors were puzzled by the absence of more specific changes and found difficulties in the interpretation of what they did

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Reprints of this entire series of articles, appearing in successive issues of the Journal, will be available through the publishers in book form following appearance of the last installment.—Editor.

*I have been unable to find documentation for the statement[10,70] that Hippocrates[51] described the Scythians as having skin and joint changes of the precise type seen in this syndrome.

find. The contribution in 1901 by Ehlers[25] of Denmark consisted of pointing out the associated loose-jointedness and the subcutaneous hemorrhages which are prone to occur. Danlos[15] in 1908 rounded out the clinical description with inclusion of the tumors which may develop at subcutaneous sites.

Fig. 1.—Job van Meekeren's case of "extraordinary dilatability of the skin."

"In the year 1657, in the presence of the very distinguished John van Horne and Francis Sylvius, professors of medicine in the famous academy of Leyden, as well as of William Piso and Francis vander Schagen, practitioners of Amsterdam, we saw in our hospital a certain young Spaniard, 23 years of age, by the name of George Albes, who with his left hand grasped the skin over his humerus and right breast and stretched it till it was quite close to his mouth. With each hand he first pulled the skin of his chin downward like a beard to his chest, hence he lifted it upwards to the vertex of his head so as to cover each eye with it. As soon as he removed his hand the skin contracted to reassume its proper smoothness. In the same way he pulled the skin of his right knee upwards or downwards, to the length of half an ell; then it easily returned to its natural position. It was worthwhile noting that the skin which covered the forementioned parts on the left side could not be extended since it firmly adhered to them. It has, thus far, not been possible to learn the cause [of this anomaly?]."—Translated from original Latin by Dr. Owsei Temkin.

Many terms have been used for this syndrome or more often for its individual features. As in the case of the Marfan syndrome, the eponymic designation seems preferable, since it does not convey any connotations of the invariable occurrence of an individual manifestation or any ill-founded notion of the nature of the basic defect. "E-D" is the abbreviated label which will be used frequently in this presentation.

This survey of E-D is based on a personal study of eight kinships, each with at least one affected person. Comparison of the findings with those reported in the literature is made.

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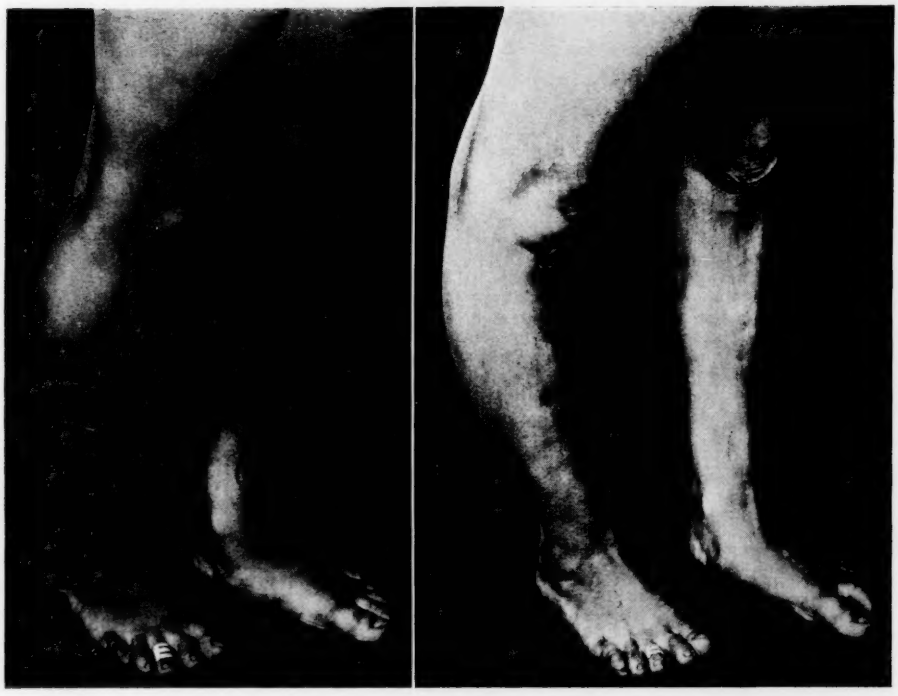

B. C.

Fig. 2.—Changes in skin and joints of 16-year-old girl, D.V. (A 41965). *A*, Cutaneous hyperelasticity. *B*, Normal position of knees. Note papyraceous scars over the knees and flat feet. *C*, Genu recurvatum, more on the right. *D*, Hyperextensibility of fifth finger. *E*, Hyperextensibility of thumb. Note in the left hand the hyperextension of the index finger and the abnormal separation of the knuckles. *F*, Hyperextensibility of fingers. *G*, Unusual mobility of hip joints is shown.

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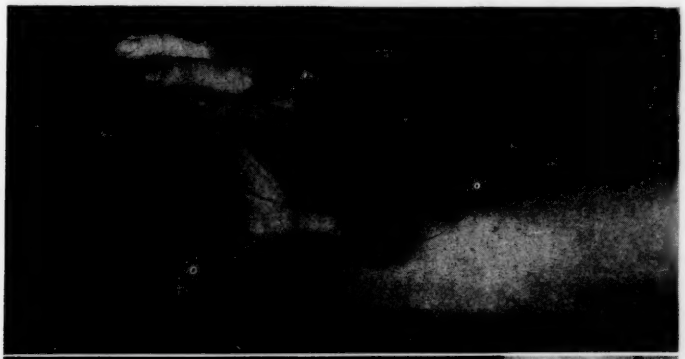

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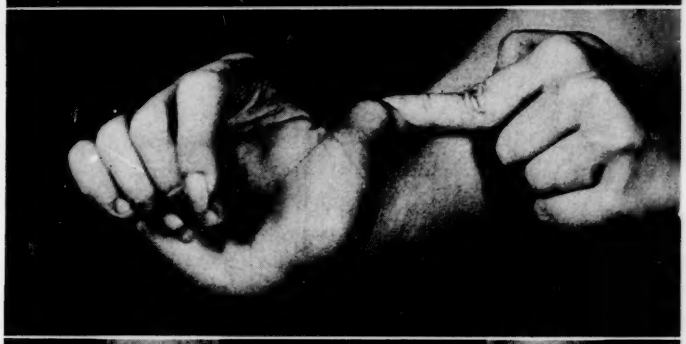

E.

F.

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CLINICAL MANIFESTATIONS[45,88]

The manifestations of the Ehlers-Danlos syndrome can conveniently be discussed under these headings: cutaneous, skeletal, ocular, and internal.

The Skin[2,11,43,72,77].—Characteristically, the skin in E-D is velvety in appearance and feel. It may also resemble wet chamois in feel. In the infant, it may be impressively white. It is hyperextensible, yet not lax (Fig. 2,*A*).

The term *cutis laxa* is inappropriate in the typical case in young persons. Except as noted below, the skin is truly hyperelastic.*

In addition, the skin is fragile and brittle. Minor trauma may produce gaping, fish-mouth wounds. One of my patients was for a time a professional boxer, a multilating occupation for one with this disorder. Another, 16 years old at the time of study (Fig. 2), had had a total of 148 cutaneous stitches taken during her lifetime. Often stitches hold poorly in the skin,[38,76] and the patients and physicians resort to the use of adhesive tape. In the patient of Brown and Stock,[9] 282 stitches had been taken before count was stopped. Thomas, Cordier, and Algan[89] described slow healing of a skin biopsy site and dehiscence of an ocular incision for removal of an ectopic lens. Packer and Blades[63] observed disruption of an appendectomy scar four times in thirty months. In one of my cases, a surgeon described the tissue at laparotomy as being like wet blotting paper. The tissues at autopsy are likely to be abnormally friable (*v. seq.*).

Very little bleeding occurs from the skin wounds. On the other hand, easy bruisability is the rule and, together with other hemorrhagic phenomena, frequently leads these patients to consult hematologists. The subsequent organization and calcification of the hematomas at times result in one type of pseudotumors.

So-called molluscoid pseudotumors[64,69] develop at pressure points—heels, knees, elbows, etc. These were the basis for the misconceived term of Hallopeau and Mace de Lépinay[15,34]: juvenile pseudodiabetic xanthomatosis. Another type of tumor, small to be sure, seen in these cases is the so-called spherule which is usually pea-sized or smaller, and slips about under the skin an inch or more, without causing the patient any discomfort. These are small fat-containing cysts which may become calcareous.[97] They are most frequently the basis for subcutaneous calcifications which may be demonstrable radiologically,[4,35] another basis being calcified hematomas as noted above. Congenital lipomatosis has been described in association with Ehlers-Danlos syndrome by Tobias.[91] It is entirely possible, however, that the fatty tumors in his case were an integral part of the connective tissue disease. At times actual ossification occurs.[41] The subcutaneous calcifications are characteristically ovoid in shape and 2 to 8 mm. in largest dimensions. They occur principally on the legs and to a lesser extent on the arms. Radiologically they display a diffuse inner calcification with a more dense surrounding shell. They are not laminated like phleboliths. These

*To the physicist *elasticity* means a restoration of initial condition after release of a distorting force. Perfect elasticity means complete recovery after deformation. An inelastic substance is one in which there is no force of restitution. For example, a steel beam is highly elastic in the scientific sense although scarcely so in the conventional popular sense. To the popular mind *elasticity* connotes only in a secondary manner the restitution of original condition. The primary connotation in general usage is stretchability. The term *hyperelasticity* must refer mainly to this latter feature. It is used to indicate a close resemblance to the physical properties of a rubber band.

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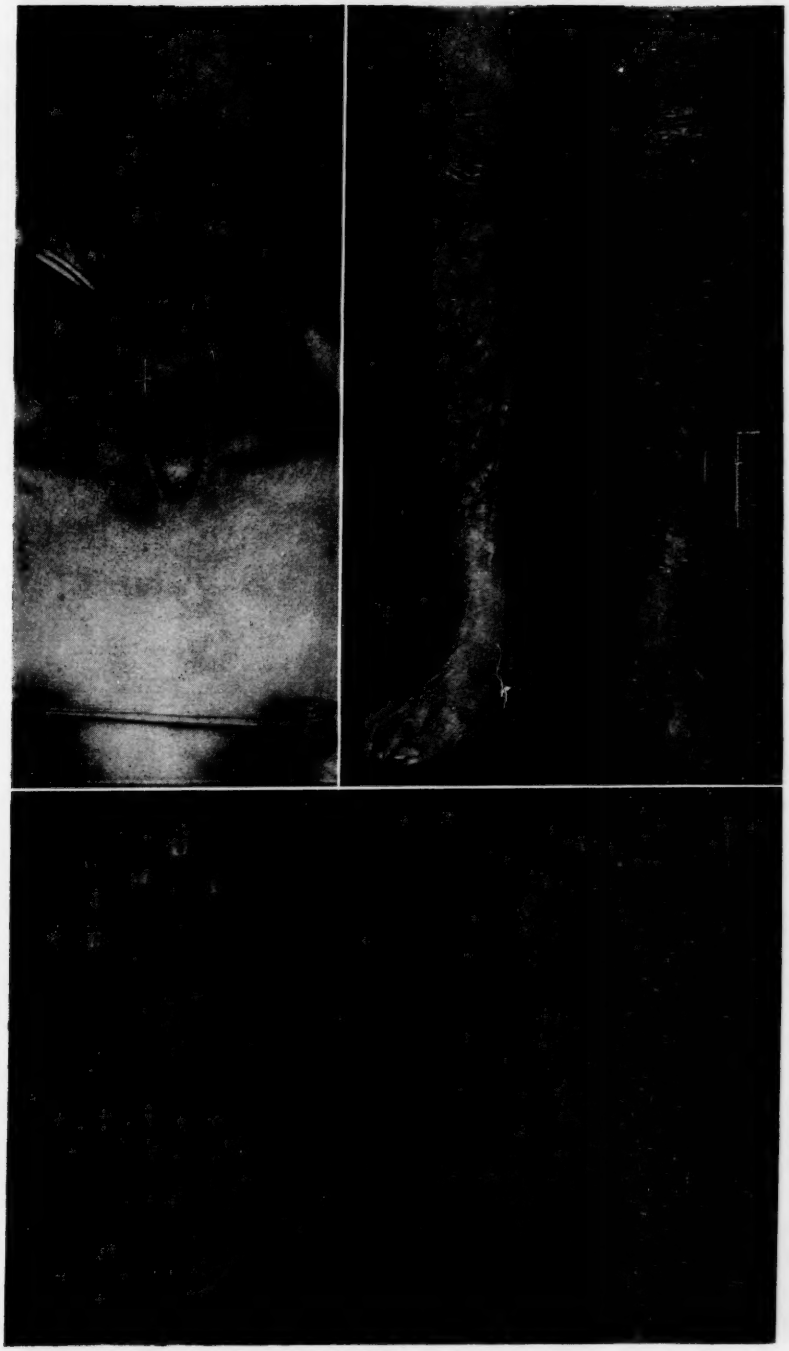

Fig. 3,*A-C.*—(For legend see opposite page.)

characteristics, together with the facts that they are not in muscle (as are calcified parasitic cysts) and are too widely distributed to be phleboliths, should permit the radiologist to make the diagnosis of E-D.

Easily recognized changes develop in the skin overlying the knees, shins, and elbows; it becomes shiny, parchment-thin, and hyperpigmented (Fig. 2). Resulting are the so-called "cigarette paper" or "papyraceous" scars. Telangiectases sometimes develop in the region of these atrophic scars. The skin changes may suggest those produced by exposure to x-rays.

Bleeding may occur from the gums with brushing of the teeth, from tooth sockets after dental extractions, from the pharynx after tonsillectomy, and at the site of operations on the joints.[95] Petechiae in late pregnancy and prolonged post-partum hemorrhage have been described.[78] Contrariwise, in one of my patients it is difficult to get blood for cell counts by finger puncture, and venipunctures are also difficult, seemingly because of very small and collapsed superficial veins. In another of my patients (Fig. 5), a strain of the tendons of the hamstring muscles at the knee resulted in the subcutaneous dissection of blood down to the ankle. E-D must be included in the differential diagnosis of familial hemophilia-like states. All tests of coagulation are usually normal except that the Rumpel-Leede test may be positive.[63]

Blisterlike lesions may develop, suggesting epidermolysis bullosa (see Weber's interpretation of Burrows' case[10]).

The limitation of the cutaneous changes, particularly hyperelasticity, to one side of the body, as recounted by van Meekeren[94] in 1682, is almost completely incredible to the reader but is lent credence by identical reports by DuBois[22] in 1931 and by Murray and Tyars[57] in 1940. Limitation of integumental hyperelasticity to the mucous membranes, specifically those of the mouth and tongue, has been described[21] and many cases have evidences of changes at these sites.[50] It is said that affected women do not get striae gravidarum.[38]

The skin of the hands and the soles of the feet tends to be redundant (unlike most of the skin elsewhere which fits snugly) and with pressure flattens out like a loose glove or moccasin (Figs. 5*A*, *C*, and *D*). A comparable change may develop in later years at the elbows, where the skin may hang lax like a dewlap (see Fig. 5,*B*). In general, late cases tend to show cutis laxa more than cutis hyperelastica, whereas, as emphasized above, cutis laxa is not an accurate designation in the typical case in young persons.

Acrocyanosis and chilblains have been described as a seemingly integral component, by French authors in particular,[26,41,56,60,82] but by others[9,12] as well. There seem to be few American reports of this complaint. In general, chilblains are much less common in this country than in Europe, possibly because of our more universal use of central heating. E-D is at least one basis for acrocyanosis which "runs in a family." It may be the presenting complaint in E-D. For example, Gilbert, Villaret, and Bosviel[29] described a 22-year-old man who had had cyanosis of the hands, feet, and ears from birth and displayed the other characteristic features of E-D. In the patient's family there were several other cases of "cyanosed limbs and ulcerated chilblains" in association with E-D. Burrows[10] provided an excellent photograph of the hand of one of these patients showing both joint hyperextensibility and cyanosis of the fingers.

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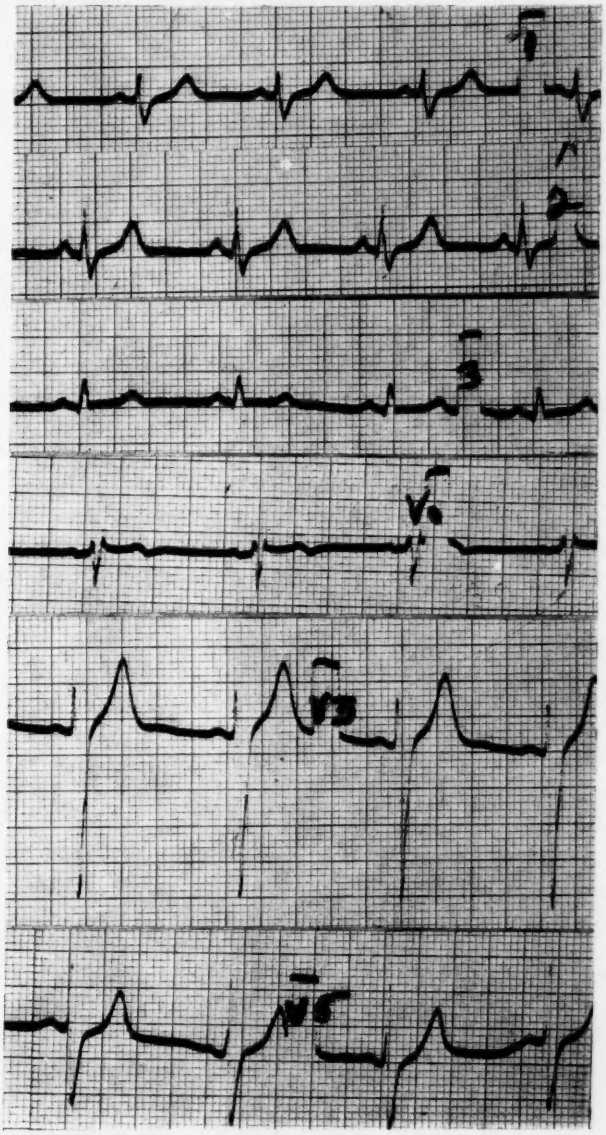
Conceivably either the abnormality with hyperelasticity of the supporting tissues about the arterioles or of the connective tissue in the vessel wall itself interferes with blood flow. My observations of difficulties in obtaining blood by fingure puncture or venipuncture (see above) are significant in this connection.



D.

Fig. 3.—Patient aged 35 years. *A*, Note scars of forehead and hyperextensibility of the skin. The patient was a professional boxer for a time. *B*, Note the spherical tumor in the skin of the anterior aspect of the left thigh. Ability to hyperextend the thumb, as in *C*, occurs frequently as an isolated, inherited characteristic.[30,100] *D*, Incomplete right bundle branch block present since at least the age of 19 years and almost certainly all of life. No other cardiovascular or internal medical disorder was demonstrable.

The Musculoskeletal System.—Hyperextensibility of the joints is characteristic (Figs. 2,*D* 2,*E*, 2,*F*, 3,*C*, 4,*A*, 4,*B*). This and the corresponding change in the skin make the victims of advanced forms of this disease the "India rubber men," "human pretzels," and contortionists of side shows. The hyperextensibility tends to become less marked as the patient becomes older. Frequently the patients have joint effusions, especially in the knees, because of traumatization as a result of the joint instability. Flat feet commonly occur from ill-fitting shoes and from what, for these patients, is excessive walking (Fig. 3,*B*). Clubfoot is described.[5] The loose-jointedness, in the knees in particular, may result in a gait and stance suggesting tabes dorsalis[42] (Fig. 2,*C*, 5,*A*). Habitual dislocation of the hip,[15,59,98] patellae,[22,59] shoulder,[65] radii,[42] clavicle,[33] and other joints is a frequent feature. As in Marfan's syndrome, the sternal ends of the clavicle may be very loose.[42] There is likely to be genu recurvatum[98] (see Fig. 2,*C*). The patients are often able to pull their fingers out longitudinally for an appreciable distance and allow them to snap back into place on release. Kyphoscoliosis is likely to develop.[16,42,59,75,87,99] Spina bifida occulta is described.[44] Arachnodactyly[41] and deformity of the pinnae also occur. Dental deformities are frequent[26,42,58] and Gothic palate may be present.[40] Muscular hypotonicity and underdevelopment seem to exist in these patients. In one of my cases, a 4-year-old child, amyotonia congenita of Oppenheim was the initial diagnosis. Smith[82] describes a similar experience. Hernias occur frequently.[97] In some, repair of an umbilical hernia at a young age is necessary.

Ectopic bone formation with formation of osseous bridges between the acetabula and the femoral trochanters have been described by Katz and Steiner.[41] The pathogenesis may have involved hemorrhage from increased joint mobility.

The Eye.—Changes have been described in the ocular adnexa, the cornea, the sclera, the suspensory mechanism of the lens, and the fundus.

The skin about the eyes often lies in redundant folds and can be pulled out to a considerable distance like the skin elsewhere. Epicanthal folds are frequent. Méténier[54] has lent his name to a frequent phenomenon, namely, unusual ease in everting the upper lid.

Blue sclerotics have been described commonly.[6,24,90] Microcornea with associated glaucoma was described in one patient[24] in whom the small size of the cornea was thought to be responsible, at least indirectly, for an impediment to occular drainage. Keratoconus is also described.[90]

Ectopia lentis occurred in at least one twice-reported patient.[89,90]

In one patient, the authors[5] described and illustrated changes in the fundus consisting of retinitis proliferans, pigment spots which were interpreted as residua of microhemorrhages, and detachment of the retina of secondary type (no retinal tear was detected).

Internal Ramifications.—The internal manifestations of E-D have not been investigated to any significant extent. Those manifestations which have been identified include (1) diaphragmatic hernia, (2) ectasia of portions of the alimentary and respiratory tracts, (3) spontaneous rupture of the lung, (4) dissecting aneurysm of the aorta, and (5) certain congenital malformations of more conventional type.

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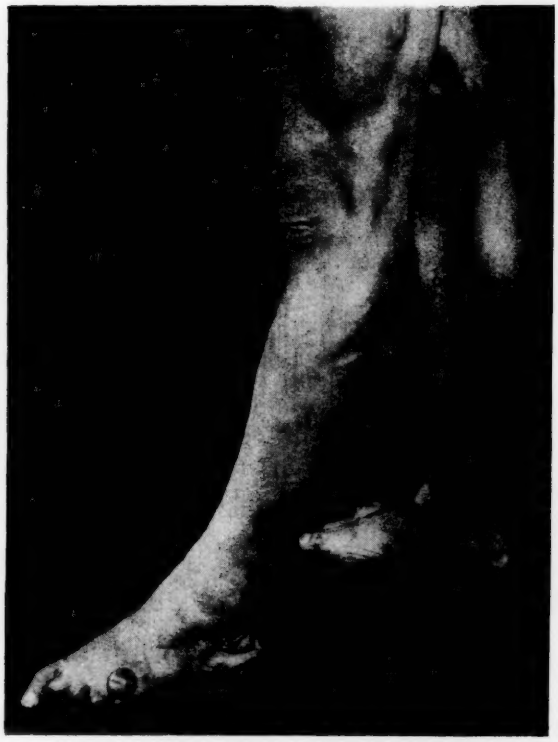
A.

B.

Fig. 4.—C. G. (287731), 47 years old. Long history of "congenital dislocation of right hip," treated with a spica at the age of 2 years and with several operations in his twenties. Bilateral inguinal hernias repaired. Hiatus hernia is apparently responsible for epigastric and substernal pressure, which occurs especially in the recumbent position and is relieved by belching. Two operations on knee for presumed trauma of automobile accident. At the age of 27 years, "relaxation of right radiocarpal joint" necessitated application of a cast. Hyperelasticity of the skin, although present, was a subsidiary feature in this patient.

A.



B.

Fig. 5.—K. W. (667280), 48-year-old man. *A*, Note deformity of feet, molluscoid tumors around heels (seen less distinctly in Fig. 2,*B*). The soles appeared to be loose-fitting and like moccasins. *B*, Dewlaps of both elbows.

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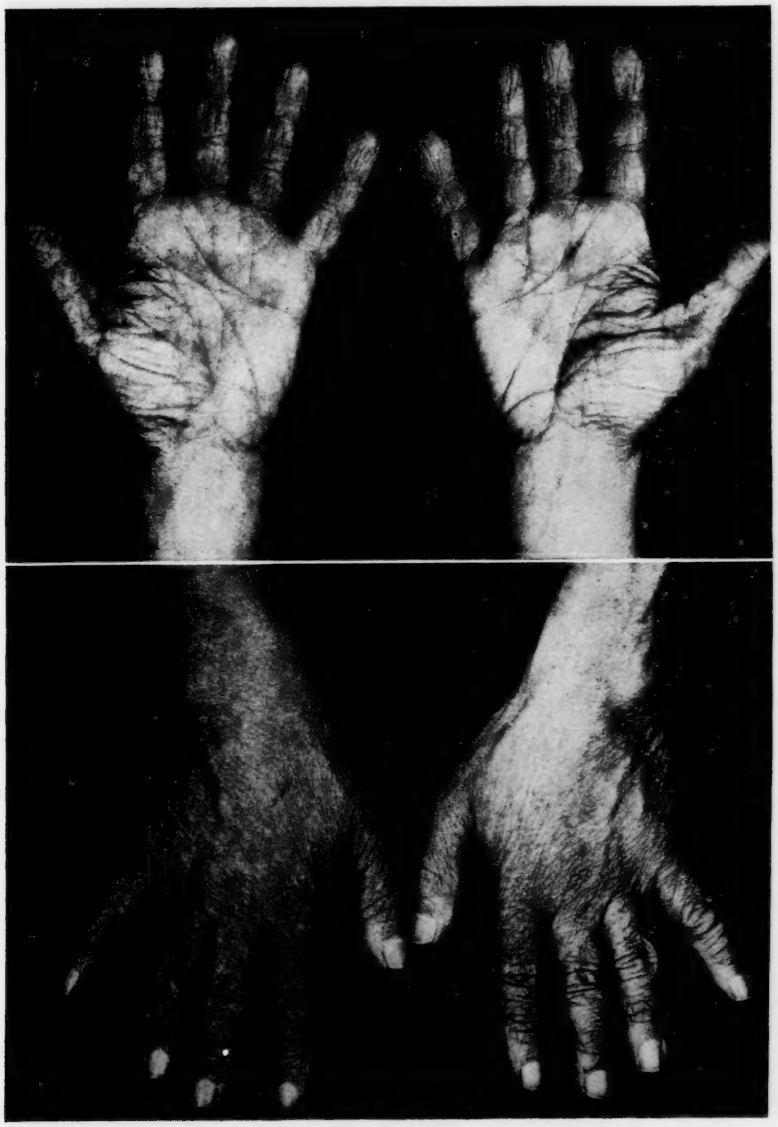
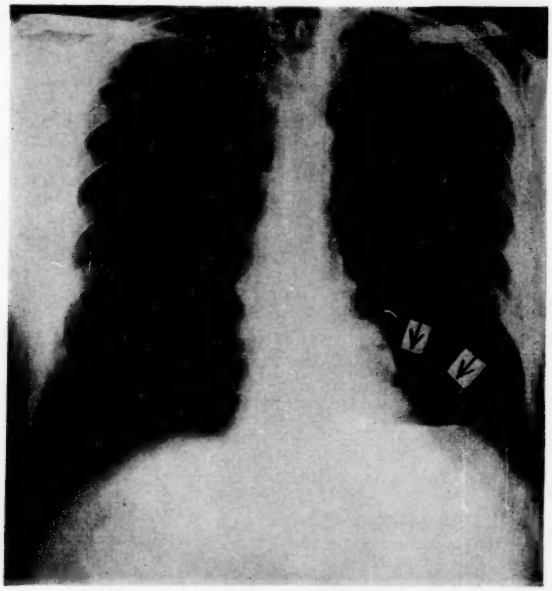
One of my patients has eventration of the left leaf of the diaphragm (see Fig. 5,*E*). Differentiation from a large posterior diaphragmatic hernia is uncertain. We have observed hiatus hernia in a second patient of whom other illustrations are shown in Fig. 4. Brombart, Coupatez, and Laurent[7] described a patient in whom hiatus hernia, diverticulum of the stomach, duodenal diver-



C.

D.

Fig. 5, *C* and *D*.—Comparable lax and furrowed skin of the hands.



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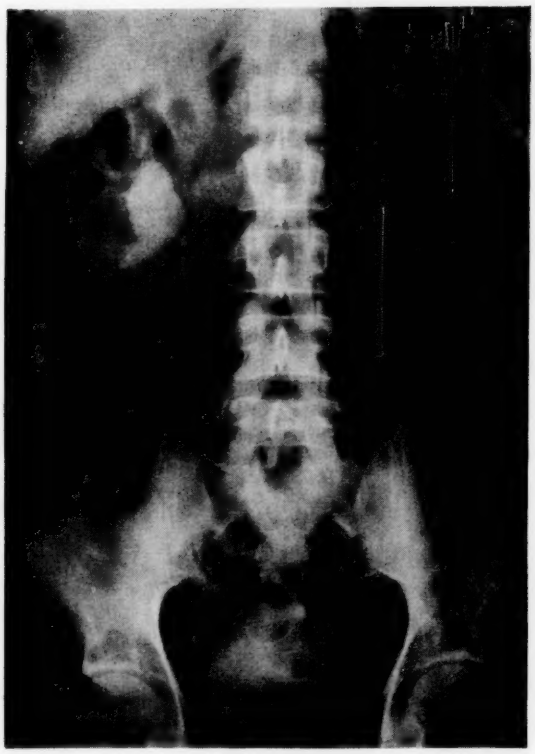

F.

Fig. 5, *E* and *F*.—*E*, Posterior eventration of diaphragm. *F*, Anomaly of ureteropelvic function, bilaterally. Nonfunctioning kidney on left.

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ticulum, and colonic diverticulosis occurred in association with E-D. Megaesophagus, megatrachea, and megacolon were described in another case.[56] Bladder diverticulum is described.[86]

In one reported patient,[63] repeated episodes of mediastinal and subcutaneous emphysema occurred, and we have observed spontaneous pneumothorax in one patient. It is to be noted that in the first case of dissecting aneurysm described below, the lungs revealed subpleural blebs, and subcutaneous emphysema was present.

Fatal dissecting aneurysm of the aorta has been observed by me in two patients in whom the diagnosis of E-D is distinctly possible. Interestingly, the histologic changes in the aorta in at least one of these were those of Erdheim's cystic medial necrosis and indistinguishable from those discovered in some cases of the Marfan syndrome. Abstracts of these two cases follow.

CASE 1.—H. L. R.,* a 15-year-old Negro student, with a history of always having been sickly, was thrown forcibly to the ground by a schoolmate. He complained immediately of pain in the chest extending down the right arm and soon developed signs and symptoms of circulatory collapse. He was taken to the neighboring office of a physician, where he died within ten minutes.

Autopsy revealed an adequately developed and nourished Negro male weighing 140 pounds and measuring 5 feet 6 inches in height. The skin showed many scars; some resembled burn scars. One on the right thigh was covered with thin epidermis and measured 15 by 3.8 cm. wide. An ulcer with hemorrhagic base, 25 cm. in diameter, was located on the medial aspect of the left ankle. There was considerable subcutaneous emphysema below the right rib margin.

During the dissection the connective tissues were found to be very friable. They tore easily and even the skeletal muscles pulled apart with incredible ease. (The autopsy was performed only a few hours after death. The tissue were not autolyzed histologically. Dr. Thoma, the prosector, had never encountered such fragility of tissues and considered it highly significant.) Fourteen hundred cubic centimeters of blood was found in the right hemithorax. The mediastinal structures were infiltrated with blood which also had dissected along the fascial planes of the neck. The lung showed multiple large emphysematous subpleural bullae and were easily torn. The heart weighed 300 grams. The gastrointestinal tract tore easily.

Histologic studies, including stains by the periodic-acid-Schiff method and elastic tissue stains, were unrevealing of definite abnormality.

Further investigations of the boy's previous health and of his family revealed that he had always been sickly, did not play as actively as his contemporaries, and often complained of severe headache. He "cut" his skin easily and healed poorly. At the age of 11 he had sprained his ankle; x-rays of the injured part were not considered abnormal on review.

The father of the patient died at the age of 21 or 22 years of asthma. The mother died at the age of 22 years after a twenty-four-hour illness, beginning with abdominal pain, nausea and vomiting, and characterized by progressive circulatory failure. Autopsy was not performed but the diagnosis given on the death certificate was "internal hemorrhage of unknown cause." There were no siblings of the propositus.

CASE 2.—J. M. M.,† a 24-year-old white man, was well until 6 A.M. on the morning of Dec. 31, 1946, when he awoke with a vague discomfort in the abdomen. In the course of two hours this developed into pain in the right flank and lower quadrant of the abdomen. By the time he was admitted to the hospital, a few hours after onset, he was in profound shock. The administration of fluids intravenously raised the blood pressure from an indeterminably low level to

*For calling this case to my attention I am indebted to Robert Osborne, fourth year student, Medical College of Virginia. For much information bearing on the case I am indebted to Dr. George W. Thoma, formerly Assistant Chief Medical Examiner, Commonwealth of Virginia.

†I am indebted to Dr. John F. Brownsberger of Takoma Park, Maryland, for much information on this patient.

90/60 mm. Hg. The white count was 25,000 and 28,000 per cubic millimeter on two determinations. The hemoglobin concentration fell from 82 to 69 per cent of normal during the afternoon. By 3 P.M. the patient was complaining of pain in the region of the right shoulder. Abdominal exploration was undertaken at 5 P.M. The abdomen contained blood-stained fluid. A large retroperitoneal hematoma involved the right kidney. There was dissection into the mesentery which was torn in several places. The surgeon compared the tissues to wet blotting paper. Bleeding and clotting times determined postoperatively were 1 and 4 minutes, respectively. The patient died at 4:15 A.M. on Jan. 1, 1947.

Subsequent investigations revealed that the patient had always bled and bruised easily. He also had sustained a number of fractures. The possibility of minor trauma during the previous evening could not be excluded.

Autopsy revealed a body measuring only 62 inches in length. Despite this, arachnodactyly was thought to be very impressive. The prosector may have been unduly impressed because of the recognized association of arachnodactyly and dissecting aneurysm. During the opening of the chest at autopsy the ribs were thought to fracture with abnormal ease. The abdomen contained 500 c.c. of bloody fluid. The aorta and the renal and iliac arteries were described as hypoplastic. A dissection of the right renal artery with infarction of that kidney was discovered. Histologically the media of the aorta was thin with numerous areas of "myxomatous degeneration" and basophilically staining material. There was some fragmentation of the elastic fibers which seemed to be normally abundant but morphologically abnormal. The renal artery showed marked fragmentation of elastic fibers.

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Although the second patient was included as an instance of arachnodactyly in reports[31,32] of a series of cases of dissecting aneurysm, the short stature, the easy bruisability, and the friability of the tissues at operation and at autopsy suggest E-D.

One reported patient had interatrial septal defect[26]; another had tetralogy of Fallot.[96] A loud systolic murmur in the pulmonary area, audible also in the left interscapular area of the back, was described in one patient.[52] One of my patients has demonstrated for many years, probably all his life, the electrocardiographic pattern of incomplete right bundle branch block without subjective or other objective cardiovascular manifestations (Fig. 3,*D*).

Another of my patients has a bilateral congenital anomaly of the ureteropelvic junction (Fig. 5,*F*). In the case of Marfan's syndrome it was pointed out that there are a number of manifestations which are congenital malformations in the conventional sense and which occur often enough to be considered bona fide components of the syndrome. It was proposed that these are secondary manifestations, that the hereditary disorder of connective tissue creates an ontogenetic setting in which certain predictable congenital anomalies occur with increased frequency. In E-D, ureteropelvic anomaly, tetralogy of Fallot, and interatrial defect may fall into this category of secondary manifestations. However, since to my knowledge, each has been described in only one patient, it is equally reasonable to suspect that these manifestations may have occurred by accident.

As a rule, mental retardation is not a feature of this syndrome. However, occasionally patients show it, probably as a coincidentally associated finding.[48,50] Severe essential hypertension occurred in one patient as a probable incidental finding.[41]

PATHOLOGY

In none of the five disorders of connective tissue discussed in this series is the microscopic anatomy in such a disputed state as in E-D.[45]

Increase in elastic tissue of the corium has been described by many writers.[1,6,38,54,55,70,71,76,83,89,91] Some of these described morphologic abnormalties of the elastic fibers, as did Smith[82] and Pittinos,[68] who, however, did not consider the elastic fibers to be more numerous than normal. Williams[102] and Pautrier[64] found the elastic fibers *normal*, and Brown and Stock[9] believed them to be *decreased*.

Diminution and morphologic abnormalities of collagen fibers have been described.[62,82,91] Katz and Steiner[41] report histochemical studies which they interpret as indicating increase of mucopolysaccharide of corium.

Jansen[36] points out, with excellent illustrations, that "in normal skin, a system of robust, well directed, crossing and tightly interlacing collagen fibre bundles is present. The whorled disorderly structure in hyperelastic (E-D) skin is remarkable; the collagen bundles seem to have been insufficiently united." By electron microscopy collagen and elastin were morphologically normal. This corrborates the finding of Tunbridge and his collaborators,[92] but Jansen was unable to agree that there was an absolute increase in the number of elastic fibers.

Collections of giant cells are sometimes found.[75] The subcutaneous nodules or spherules are apparently fat-containing cysts.[97] They frequently become calcified. It seems likely that they are related to minor traumata and to the general fragility of the connective tissue in which the fat deposits normally exist.

How much of the bleeding is due to a defect in the supporting tissues and how much due to weakness of the vessel walls themselves is not clarified by histologic studies. Abnormal, dilated, weak-appearing vessels have been described by Tobias[91] and others.[50]

Unfortunately, studies of tissues other than skin have not been reported with the exception of an autopsy case described by Leinhart[50] and, of course, the two cases of dissecting aneurysm described above. In Leinhart's patient, a 22-year-old woman who died of pulmonary tuberculosis, no internal abnormality referable to the connective tissue defect was discovered.

THE BASIC DEFECT

Superficial consideration of the clinical manifestations of E-D might suggest an abnormality of elastic tissue as the fundamental defect, probably a superabundance of elastic fibers in the skin and joint capsules. However, the histologic studies by no means afford unequivocal substantiation of this theory. Brown and Stock[9] suggested, and others (notably and most recently Jansen[36]) maintain,[28] that the defect may reside in the collagen fibers which, because of lack of normal tensile strength, permit the skin, joint capsules, ligaments, and so forth, to be stretched beyond the normal limits. The elastic fibers may function in connection with the process of restoration to normal configuration of these tissues. According to the "collagen theory," the histologic changes, both

quantitative and qualitative, are interpretable as secondary effects of the abnormality of collagen. I am inclined to favor the view that the Ehlers-Danlos syndrome is another heritable disorder of collagen, biochemically, morphologically and clinically distinct from the others which are under discussion in this series.

The comparative inextensibility of normal collagen may depend upon some specific molecular or intermolecular structure which is altered in E-D with resulting increase in extensibility. This is assumed to be the case in the theory of Brown and Stock and has been explicitly stated by Froelich[27] and others. Jansen[36] has recently advanced a related theory incriminating collagen but placing the defect at a higher level of organization of collagen, i.e., that E-D is a disorder of the organization of collagen fibrils into bundles and of the bundles into a strong network. He refers to the disease as one of a "defective wickerwork" of collagen. The evidence he assembles (see above, under Pathology) and the clinical aspects of the disease outlined here make Jansen's version of the "collagen theory" highly probable.

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It is possible that in some patients and at some subcutaneous and articular locations production of an excessive member of elastic fibers is stimulated by the repeated and excessive stretching. In tissue culture, Maximow[53] and Bloom[3] thought the tugging of contractile myocardial cells was a factor in the formation of elastic fibers.

The changes in the skin of the feet and hands and at the elbows of older patients fit in well with the view that the primary defect resides in the collagen fibers: the normal elastic tissue may, with the passage of time, "wear out" from excessive stress imposed upon it, and the cutis laxa (as opposed to cutis hyperelastica) of late cases become evident.

INCIDENCE AND INHERITANCE

Thus far, this syndrome has been described principally in Europeans and persons of European extraction. There is one report from India[12] of the disease in a 12-year-old Hindu girl. I know of no report of the condition in Negroes and have encountered the disease in only one possible instance, the first case of dissecting aneurysm above.

Schaper[79] stated in 1952 that only 93 cases of this syndrome had been reported. Although the number is now probably well in excess of 100, it is possible that fewer of these cases have been reported than of any of the other syndromes discussed in this series. This is in part the result of greater difficulties of recognizing the syndrome, since cutaneous and articular hyperelasticity is a graded trait. I hazard to say, however, that in actuality this is one of the most frequent of the heritable disorders of connective tissue. My photographer, in the course of the study of other patients with E-D, recalled that his brother-in-law could do contortionist tricks with his hands. On investigation this individual was found to have had congenital dislocation of the right hip, bilateral inguinal hernias, diaphragmatic hernia, trouble with one knee and the right wrist (Fig. 4). Although these had all been considered unrelated, the diagnosis of the Ehlers-Danlos syndrome is quite certain and all these manifestations are clearly part of the syndrome. This patient illustrates how easy it is to overlook the generalized disorder.

The incidence of this syndrome, at least the frequency with which the diagnosis is made, relative to that of other heritable disorders of connective tissue, is indicated by the fact that available to me for study have been only eight kinships in which at least one bona fide instance of E-D has occurred, whereas over fifty Marfan kinships, forty to fifty osteogenesis imperfecta kinships, sixteen pseudoxanthoma elasticum kinships, and fifteen kinships with the Hurler syndrome have been collected by tapping all possible sources of index cases.

In at least three of the eight kinships I have studied, more than one affected person was identified: father-daughter; mother-son; mother-mother's cousin-daughter. Since mild manifestations tend to be overlooked by laymen and since only the propositus was examined in several instances, the above evidence can be taken only as a rough indication of the pedigree pattern which may be observed.

Johnson and Falls[38] reviewed sixteen families reported in the literature as having more than one affected member.[33,44] In these families, a total of eighty affected individuals had been identified, of whom exactly half were male. Brown[8] found nineteen affected members in a family numbering forty-seven individuals. Johnson and Falls[38] studied the pattern of inheritance in detail and concluded that the disorder is inherited as a dominant. Two sisters with an unusually severe form of the disease were children of cousins, each with a mild form of the disease; this suggested to the authors that the trait might have occurred in homozygous state in these girls. Consanguinity was thought to be a factor in the cases observed by Ronchese[76] and by Weber and Aitken.[97]

Coe and Silver[13] presented illustrations of members of three generations displaying the E-D syndrome, and Stuart[84] traced it through four generations. Here there was again clear evidence of dominant inheritance. The disease has been described in one of twins who were probably fraternal.[20] A number of pedigrees[95] have been reported since 1949 when Johnson and Falls collected 16 kinships with more than one case.

Penetrance in this disease is probably considerably lower than in Marfan's disease, for example. This, however, is merely the result of the greater difficulty of recognizing mild and graded abnormality of the joints and skin as opposed to less equivocal manifestations, e.g., ectopia lentis, in Marfan's syndrome.

MISCELLANEOUS CONSIDERATIONS

"Simple" hypermobility of joints, known also as congenital laxity of ligaments, may occur as an isolated finding[42,73,85] with a genetic background distinct from that in E-D. For example, in Key's family[42] a sex-linked inheritance was suggested; the disorder occurred only in males. Loose-jointedness occurs also in the Marfan syndrome and with osteogenesis imperfecta, whereas reduced joint mobility is characteristic of the Hurler syndrome. In the differential diagnosis of loose-jointedness, especially in children, cerebrocortical degeneration or malformation, mongolism, cretinism, rickets, and nonspecific cachexia must be kept in mind.

Blue sclerae are not uncommon in E-D,[6,24] and presence of this feature cannot be taken as evidence of associated osteogenesis imperfecta. The description[50,74] of associated dolichostenomelia (long, thin extremities as in the

Marfan syndrome) cannot be taken as evidence that E-D and the Marfan syndrome coincided in those patients, since no ectopia lentis was detected and no unequivocal cases of the Marfan disease in other members of the family were described.

At least three seemingly bona fide instances of coincident E-D and pseudoxanthoma elasticum have been described.[14,59,65] In Cottini's patient[14] there were angioid streaks and lesions of the skin of the neck characteristic of pseudoxanthoma elasticum (see Section VI of this series) and, in addition, cigarette paper scars of the elbows and knees and hyperextensible skin and joints characteristic of E-D. The pseudoxanthoma elasticum, which appears to be a recessive trait, was not transmitted to a daughter who suffered from acrocyanosis or a son who had hyperextensible skin and joints, hernia, and varices of the leg veins. The 22-year-old woman described by Pelbois and Rollier[65] consulted them because of the cosmetically undesirable lesions of pseudoxanthoma elasticum involving the skin of the neck and other areas of flexure. As well as angioid streaks of the fundus (characteristic of pseudoxanthoma), the patient had multiple cicatrices indicative of cutaneous fragility, striking cutaneous hyperelasticity, and articular hypermobility. The parents were first cousins, a fact significant in the appearance of the recessive trait, pseudoxanthoma. The parents were themselves unaffected by pseudoxanthoma although a maternal aunt of the patient was affected. As for E-D, the patient's mother displayed features of this syndrome and had probably transmitted it as a dominant trait to her daughter. These are then examples of accidental coincidence of the two syndromes, one behaving as a dominant and one as a recessive trait.

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In one patient, 61-years-old,[58] E-D coexisted with muscular atrophy of the Aran-Duchenne type (amyotrophic lateral sclerosis). I find it impossible to agree with the authors[58] that an etiologic connection between the two conditions existed. In one of my cases, Oppenheim's disease (amyotonia congenita) was the original diagnosis when the patient was first seen at the age of 4 years. Abnormality of creatine meatoblism was reported in one patient[68] and in another[66] there was coincident parathyroid tumor with osteitis fibrosa cystica. After correction of the hyperparathyroidism surgically, it appeared that the joint laxity, particularly the scoliosis, and the fragility of the skin decreased.

Interesting physiologic studies of skin elasticity and tensile strength have been done in recent years.[18,19,38,46,60,75,99] Rollhäuser[75] found least tensible strength in the skin of infants under 3 months (about 0.25 kg. per square millimeter); more in adults (about 1.6 kg. per square millimeter) and yet more in aged individuals (over 2.0 kg. per square millimeter). With aging, furthermore, skin became progressively less extensible. These observations may explain the tendency for the cutaneous fragility and extensibility in E-D to become less striking as the affected individual ages. Rollhäuser[75] studied the skin tensile strength of a 35-year-old man with E-D and found it to be very low (0.34 kg. per square millimeter). It is of interest that this worker found parallel changes in the tensile strength and extensibility of tendons, suggesting that the properties measured in the skin may be constitutional and generalized. Wenzel[99] found lesser tensile strength in female skin and made important observations indicating

reduction in the strength of the skin in normal pregnancy and in Cushing's syndrome. In connection with the latter condition, it is noteworthy that the fragility of the skin and easy bruisability are rather similar in E-D and in Cushing's syndrome.[47] However, in all likelihood, the similarity is only superficial.

SUMMARY

On the basis of eight kinships containing at least one previously unreported case of the Ehlers-Danlos syndrome, and on the basis of the cases reported in the literature, the cardinal manifestations of the syndrome can be said to be hyperelasticity and abnormal fragility of the skin and hyperextensibility of joints. Other cutaneous and skeletal manifestations which are an integral part of the syndrome are discussed as well as ocular and internal manifestations.

It is suggested that dissecting aneurysm of the aorta may be a complication of this connective tissue disorder as well as of the Marfan syndrome. Diaphragmatic and other types of hernia occur fairly often and conventional types of congenital heart disease and congenital anomalies of the kidney have been observed. Rupture of the lung with mediastinal emphysema and/or pneumothorax appears to occur with increased incidence.

The best information appears to indicate that the basic defect is one of the organization of collagen bundles into an intermeshing network.

The disorder is probably inherited as a Mendelian dominant.

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THE CONTRIBUTION OF VOLUNTARY HEALTH INSURANCE

I. Health Insurance Fundamentals

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*From the Health Insurance Council**

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HOW to meet the costs of hospital and medical care, as well as family living expenses, is a serious problem confronting many persons with chronic disease. Voluntary health insurance is contributing a partial, but increasingly significant, answer to this question for an increasing proportion of the chronically ill.

This article, presenting some basic information about voluntary health insurance, is the first in a series of three articles on the contribution of such insurance toward meeting the financial needs of the long-term patient. The second article in the series will focus on the contribution of the older or customary types of voluntary health insurance, while the third will center on the broad new type of protection, major medical expense insurance, and its potentialities of aiding the chronically ill. The remaining articles will appear consecutively in the next two issues of the Journal.

THE INSURANCE CONCEPT AS APPLIED TO CHRONIC ILLNESS

It may be helpful, at the outset, to look briefly at the basic nature of insurance and at the use of insurance to meet the costs of chronic illness.

Nature of Insurance.—While health insurance has unique problems of its own, it is basically a branch of insurance in general. In health insurance, as in other branches, the central idea is this:

1. Relatively small, regular premiums are paid into an insurance fund by or for a large number of persons subject to a given hazard or group of hazards.

2. The money thus assembled is used to provide economic recompense for the relatively few persons who actually are stricken by a hazard insured against.

The essential function of an insurance company is to serve as a mechanism to put this plan into effect. However, it should be realized that, from a legal standpoint, the company enters a separate contract with each policyholder, the policyholders not contracting with one another.

*The Health Insurance Council, in whose behalf this article was prepared, is an organization serving to coordinate activities of the insurance business with doctors and hospitals in fostering voluntary health insurance. Its membership consists of the associations in the insurance business whose members are insurance companies interested in accident and health insurance. The author, Mr. Kendrick, is regularly on the staff of the Life Insurance Association of America, one of the Council's members.

In the long run, nevertheless, the aggregate premiums collected by the company must be enough to support the aggregate benefits offered. At the same time, the force of competition among insurers tends to keep premiums at the minimum necessary to support the benefits. So, in long-run terms, reduced benefit payments mean lower premiums while higher payments mean higher premiums. Health insurance then, in a nutshell, is a means by which people can join with one another to meet financial costs or losses of illness and injury.

Insurance and Chronic Illness.—The risk-sharing function of insurance is of greatest value when the risk insured against is a very serious one and when its occurrence is infrequent. Any insurance operation necessarily involves administrative expenses. Such expenses should not be incurred in the process of paying only nominal amounts of benefits to a large percentage of those who are insured, but rather by paying substantial benefits to a small percentage who incur severe losses.

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In fact, the view sometimes expressed that health insurance should fully meet all costs of ill health, and reimburse in full for lost income, is not valid. On the contrary, the more modest purpose of health insurance can be simply stated as being to provide timely benefits in sufficient amount to prevent ill health or accident from spelling financial hardship to individuals and families who would otherwise suffer such hardship.

From the family's standpoint, the costs of relatively frequent, minor sicknesses and injuries can best be allowed for in the family budget. If such allowance is made, no real financial difficulties are likely to develop, at least none that could be appreciably eased by the use of insurance methods. In fact, there is but little more reason to seek to insure against minor, recurring health outlays than to seek to insure against one's grocery bills or any other regular expense.

One of the chief methods of separating budgetable items from more serious financial blows is through the use of "deductibles" (a familiar feature in automobile liability insurance). In health insurance, a deductible can take various forms, such as a specified amount of money, a specified number of doctor's visits, or a specified number of days of sickness.

For example, a policy may exclude any payment for the first three doctor's visits on one illness. Again, the policy may exclude any payments for bills aggregating less than $50 or $100, and may reduce larger claims by such an amount. Many families can meet expenses of $50 or $100 out of regular income or savings, and in such cases the deductible should not place too great a strain on the family's finances. Moreover, deductibles generally enable the same premium to purchase much larger benefits, payable in case of the more serious, long-term illnesses.

PROGRESS OF VOLUNTARY HEALTH INSURANCE

In the last two decades, voluntary health insurance has moved forward at a spectacular rate. Quantitatively, coverage has increased from just a few million persons twenty years ago to more than 101 million with at least some type of voluntary health insurance at the end of 1954. Qualitatively, there

has been comparable progress. In contrast with the less liberal policies of earlier times, insuring organizations nowadays offer many attractive policies providing broad protection against serious illnesses.

Despite this recent progress, there are still millions of persons who need health insurance but who have not yet acquired it. Similarly, many people possess policies protecting mainly against minor illnesses rather than the newer policies designed primarily to protect against serious, long-term illnesses. As these facts suggest, health insurance has by no means yet realized its full potentialities toward meeting the financial needs of the long-term patient. But much has already been accomplished, and the future outlook is bright.

Moreover, apart from the prospects for future progress, the insurance protection already in force will become increasingly valuable for those who in the future fall victim to chronic disease. The point here hinges on the fact that health insurance as it exists today is a result of phenomenal growth over the past two decades. The people now covered are largely those who, in recent years, have met the qualifications for insurance. On the other hand, those who are now suffering from chronic diseases or impairments have, in many cases, become ill or reached advanced age before health insurance was so generally available and so widely purchased. *Consequently, the insurance currently in force will furnish much greater protection for the next generation of the chronically ill than it does for those now ill.*

CLASSIFICATIONS OF VOLUNTARY HEALTH INSURANCE

Within the scope of the term "voluntary health insurance" are included numerous different kinds of contract. These contracts can be classified from various standpoints: (a) by the health hazard insured against, (b) by the form in which benefits are paid, (c) as group and individual policies, and (d) as cancellable and noncancellable policies.

Hazards Insured Against.—Classified by the hazard insured against, voluntary health insurance is usually divided into five types: hospital expense protection, surgical expense protection, regular medical expense protection, major medical expense protection, and protection against loss of income.

Information on each of these types of protection, all of which can be of value to the chronically ill, will be given in the two ensuing articles of this series. However, it may be noted here that a single health insurance policy may provide two or more of these five types of protection.

Forms of Payment.—With regard to the form in which benefits are paid, there are noteworthy distinctions among (1) the policies ordinarily used by insurance companies, (2) the subscription contracts featured by Blue Cross, Blue Shield, and similar plans, and (3) the contracts used by some independent, usually cooperative plans. The insurance company contracts provide cash benefits to the policyholder or insured person. The other two types of contract, although differing considerably from each other, are both considered to provide "service benefits."

The chief differences among the three types of contract center around differing relationships among the three interested parties: the insuring organi-

zation, the policyholder or insured person, and the individual or organization (usually doctor or hospital) that actually furnishes the services.

Ordinarily, an insurance company contract is entirely between the company and the policyholder or insured person. There is a flow of cash from those insured to the company in the form of premium payments, and a reverse flow of cash in the form of benefits. The insured individual may select the person or organization he wishes to have render services to him and may make his own arrangements as to the price he will pay, the company taking no part in these relationships.

This simple type of two-party relationship is not confined to insurance companies, but also exists, to a limited extent, in Blue Cross and Blue Shield plans. Thus, if a Blue Cross subscriber goes to a hospital not affiliated with Blue Cross, cash benefits are usually paid. In Blue Shield, the subscriber whose income exceeds a specified amount usually receives cash benefits. However, for the most part, Blue Cross and Blue Shield contracts involve the three interested parties in somewhat closer relationships than do the cash-benefit arrangements of the insurance companies.

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Ordinarily, with Blue Cross and Blue Shield, there are not only contracts involving premiums and benefits between those insured and the insuring organization, but there are also contracts between the insuring organization and the persons or institutions who are to supply the services, specifying the services to be provided and the cash payments to be made in return. Thus, the insuring organization acts on behalf of those insured, to an extent, making arrangements as to the services they may receive and the price or fee to be paid.

The effect, so far as the subscriber is concerned, is to provide him with what can be called "full-payment" protection, subject to such limitations and exclusions as are specified in the subscription contract. The term "service benefits," when applied to Blue Cross and Blue Shield subscriptions, is not strictly accurate because the plan does not guarantee that the subscriber will be able to obtain service. Blue Cross, for example, does not guarantee to obtain needed hospital accommodations for its subscribers, but merely to pay the hospital in full, under the terms of the contract, for such accomodations as the subscriber or his physician may obtain.

Most of the independent plans, sometimes called "consumer-sponsored" plans, offer contracts that provide service benefits in the full sense of the term. Those who are to render the services are usually placed directly on the payroll of the organization offering the insurance, either on a straight salary, a fixed amount per patient, or other basis. Likewise, the insuring organization may be the direct owner of the hospital or other facilities to be utilized in rendering the services.

Group and Individual Insurance.—The third method of classifying health insurance is group insurance as opposed to individual contracts. Protection for the dependents of the primarily insured persons, incidentally, can be had in either case. In group insurance, the "master policy" is usually between the insurance company and an employer, but the contract gives protection to the employer's employees, and often to their dependents. In recent years, group insurance

methods have been applied to groups other than the employees of one employer. For example, the members of various farmers' organizations have been covered under group policies, and, in fact, the new techniques are of great value in extending health insurance protection to rural areas.

Group insurance, viewed broadly, is a wholesale, low-cost method of furnishing protection to the employed population. The group method is used not only by insurance companies but also by Blue Cross, Blue Shield, and most other health insuring organizations. In fact, most such organizations rely primarily on group underwriting techniques.

However, some people are not connected with an insurable group and hence are beyond the reach of the group method. Also, the group insurance of many families does not cover both income loss and the various types of hospital and medical expense. Thus, there will be a continuing need for the individual and family policies of insurance companies, which furnish protection on a "retail" basis, so to speak, both to provide protection for those not having group insurance and to provide supplementary benefits for those whose needs are not fully met through the group approach.

Cancellable and Noncancellable Insurance.—The fourth classification of health insurance draws a distinction between cancellable (or nonrenewable) insurance policies and subscription contracts, and the noncancellable policies provided by a growing number of insurance companies.

In general, cancellable policies and subscriptions are contracts which will be continued in force for a succeeding year, or other specified period, only if the insuring organization and the insured person so agree. In contrast, the insurance company guarantees to renew a noncancellable policy year after year, upon payment of the premium by the policyholder, until he reaches some specified age such as 65. Of course, neither a refusal by the insuring organization to renew a cancellable contract, nor a literal cancellation with a premium refund, can ever operate to prevent the payment of full benefits on any claim originating while the contract was still in force.

History has indicated there is a place for both cancellable and noncancellable health insurance. All Blue Cross-Blue Shield subscriptions are on a cancellable or nonrenewable basis as are most insurance companies policies currently being issued. However, recent years have seen a reawakening of interest in noncancellable insurance, not only on the part of insurance companies but also on the part of those purchasing health insurance. Noncancellable policies, it should be noted, can be of special value for those with chronic illnesses of intermittent nature.

Because noncancellable policies assure lasting protection, they ordinarily require higher premium rates. However, the right of cancelling a cancellable subscription or policy is seldom exercised, often only if the subscriber or policyholder appears prone to claim benefits when their payment is not morally justified.

SUBJECTIVE QUESTIONS IN HEALTH INSURANCE AND THE PROBLEM OF CONTROL

Most of the difficulties encountered in developing successful health insurance policies and plans stem from the human or subjective side of illness. Collectively,

these difficulties create what can be termed the problem of control. It may be helpful to examine this problem with some care as well as the alternative solutions that have been developed.

Subjective Aspects of Health Insurance.—As physicians know, human health is a very complicated matter. Most doctors recognize agreement cannot always be expected on answers to such questions as: Does the patient need to go to a hospital? Is a private nurse needed? May the patient now return to work?

The patient's appraisal of his own condition is subject, of course, to much wider variation than is medical opinion. Among several persons having the same condition, so far as can be determined by objective tests, one may shrug it off and go to work as usual. Another may take to his bed. Still another may make an emergency call to his family physician, while a fourth may demand to to go to a hospital.

There are also subjective implications connected with insurance benefits. Some who would go to work, in the absence of benefits, will remain at home if benefits are payable. Likewise, some who would not call the doctor, in the absence of insurance, will do so if benefits can be had.

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In general, the tendency of health insurance to increase the public's demand for health care is not undesirable. On the contrary, with earlier and more adequate attention, the illness may be less serious, and complications may be avoided.

But certainly, the reduction of monetary restraints by health insurance tends in some measure to increase needless work absences and unneeded hospital and medical care. Even in such cases, outright fraud is seldom involved. Usually it is just that the individual is encouraged, more or less unconsciously, by the insurance to carry his normal concern about his health to an extreme.

The Control Problem in Essence.—In devising workable health insurance plans, insurance companies are confronted with the broad problem of dealing fairly and reasonably with these subjective considerations.

On the one hand, the companies are willing and able to pay policy benefits whenever they serve a necessary and useful purpose. On the other hand, they do not wish to pay unnecessary benefits and cannot afford to do so to any substantial extent. For them to pay very many needless benefits would mean that premium charges would have to go up without any increase in the true value of the benefits offered.

Consequently, the problem of control arises: the problem of how health insurance may best provide benefits when needed without providing benefits when not needed. It may be added that this problem, obviously, is faced not only by insurance companies but also by Blue Cross, Blue Shield, and all other health-insuring organizations.

Defining Risks and Specifying Benefits.—The development of a careful statement of the risks which the policy insures against, and of the benefits payable under it, is the first step toward solving the control problem. Carefully outlining the scope and benefits of the policy, of course, does not make certain all benefits paid will be of real value, but it does serve to define the area within which the problem exists.

Another factor in determining the provisions of a policy is the size of the premium required. It should be realized that some low-cost policies, with

limited benefits, are provided for those not able or not choosing to purchase fully adequate protection. While health insurance sales representatives ordinarily urge prospective purchasers to buy fully adequate policies, final decision of course is up to the purchaser.

With reference to policy terms, a word is in order about the "fine print." While many users of this expression may merely be referring to policy restrictions and limitations generally, there may be others who have the notion that such provisions are literally written in small type. Actually, health insurance policies are printed in large type, and it is illegal for any policy to give more prominence to its positive benefit provisions than to the restrictions and limitations it may contain.

Of course, insurance policies and service-plan contracts do contain some restricting or limiting provisions, at least to the extent necessary to spell out the risk insured against. Other limiting provisions are not ordinarily found in group insurance, which even provides benefits with respect to pre-existing illnesses. In the case of individual and family policies, however, the safeguards inherent in group underwriting are lacking. Consequently, a few limitations are essential in such policies, while a few others are considered desirable by many companies.

For instance, an individual policy may restrict the benefits payable in case of an aviation accident which occurs in other than scheduled passenger flying. While restrictions of this sort are sometimes considered detrimental to the policyholder's interests, they actually are intended to protect the average or typical policyholder against unnecessarily high premiums. It would be unfair to the typical policyholder, who does not engage in amateur aviation, to increase his premiums in order to provide benefits for those who do.

From a broad viewpoint, insurance men recognize that the amateur flyer, to continue the example, may well need insurance protection against his special risks. However, they also recognize that such protection should not be provided through regular policies at regular premiums. The indicated solution is the development of special policies with high enough premiums to support the benefits offered. Insurance companies have made encouraging progress toward developing such policies.

Overinsurance and Coinsurance.—In any field of insurance, overinsurance is present if the policy benefits are more than sufficient to cover the losses suffered or the expenses incurred. For example, if a hospital expense policy provides a $15 daily "room and board" benefit, the policyholder would be overinsured if, in his locality, satisfactory hospital accommodations could be obtained for less.

The point at which overinsurance begins is often difficult to determine. For example, if a man's "take-home" pay is $70 a week, overinsurance would clearly be present if his loss-of-income policy provides benefits of larger amount. On the other hand, suppose that his policy provides $65 a week; suppose also that, as he recovers from an illness, he feels he would rather continue to rest at home, drawing benefits, than return to work for the sake of the small difference in income. In such a case, the temptation to protract the convalescence period unduly is essentially the same as if the weekly benefit had been over $70. Something closely akin to overinsurance is present—something that goes to the heart

of the basic control problem. Insurance companies rely largely on the coinsurance principle in dealing with this "something."

The term "coinsurance" signifies a sharing of the risk by the insured person and the insuring organization. In major medical expense protection, a specific coinsurance percentage is usually specified in the policy. The coinsurance principle is also employed in the customary types of health insurance, although not in terms of an explicit percentage. For example, a surgical expense policy may provide a benefit of $150 for an appendectomy, although it is known that the customary surgeon's fee in the particular area is about $200.

The point is that when the coinsurance principle is applied, either explicitly or implicitly, the policy benefits are not meant to recompense the individual completely for his income loss or his medical expenses. As a coinsurer he is expected to carry a portion of the risk himself.

In general, the insurance company endeavors to set the benefits available under a policy type at as high a level as possible, while still leaving an adequate incentive to the insured person to avoid unnecessary work absences and needless health expenditures. But in any case, the fact that for the insured person to incur needless bills would be against his direct self-interest as a coinsurer serves as a key means of solving the control problem, thereby enabling the companies to be largely successful in providing benefits when they are desirable while preventing the payment of needless benefits.

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Coinsurance and Service-Benefit Plans.—From time to time, cash-benefit health insurance is criticized for invoking the coinsurance principle. An unfavorable contrast is made with full-payment or service-benefit arrangements, which ordinarily do not leave an uninsured margin within the scope of the coverage.

However, as has been seen, the primary purpose of coinsurance is to enlist the financial self-interest of the participants in the insurance in preventing the payment of needless benefits. But the furnishing of needless benefits is equally harmful to the interests of the participants, whether the benefits are in the form of cash or not. So, "service-benefit" plans must utilize some equivalent of coinsurance in order to cope with the control problem.

In Blue Cross and Blue Shield, the participating hospitals and physicians often agree that, if the aggregate subscription fees received prove inadequate to compensate them at the stipulated rates, they will accept *pro rata* reductions in their remuneration. By such agreements, the hospitals and physicians become the ultimate underwriters or reinsurers of the plans they are affiliated with and hence have a direct incentive to prevent overutilization of their services.

In practice, this theoretical possibility of control in Blue Cross and Blue Shield is not always adequate to check excessive demands for hospital and medical care. If x-ray and other ancillary services, for example, are available to the patient at no added cost, there is little incentive for him to exercise restraint. The eventual effect of any lack of success in solving the control problem is, of course, to increase subscription charges for participants generally.

The Individual's Capacity to Coinsure.—Apart from the question of whether those considering the purchase of health insurance are willing to assume a portion

of the risk as coinsurers, there is the question of whether they are able to do so. While it is sometimes contended that most 'people are not able to bear any portion of their health expenses, this contention is hardly realistic. For one thing, no type of health insurance can be really meaningful for persons who are not normally self-supporting and who consequently are unable to pay premiums. The self-supporting people for whom health insurance does have real meaning normally have both regular income and some savings, a portion of which may be budgeted for prospective health expenses. To the extent this is done, coinsurance is entirely practicable.

In some cases, a portion of the bill may remain unmet. In such cases, it is usually feasible for the insured persons to make use of some postpayment arrangement. Installment purchasing and other types of postpayment are common features of our general economy, and are not without value in the health field.

DETERMINING HEALTH INSURANCE PREMIUMS

In health insurance, as in other fields of insurance, premiums comprise two elements: (a) *the pure premium*, an amount calculated on an average to cover exactly the cost of the benefits offered; and (b) *an expense and safety allowance*, which is intended to cover an equitable share of the necessary operating costs of the insurance, together with a small margin for safety and profit.

Pure premiums are directly proportionate to the likelihood of the hazard's occurring and to the benefits that would then be payable. Because this proportionate relationship is not greatly affected by the expense and safety element, it does not ordinarily pay to look for bargains in health insurance. The best bargain is a policy that fits the family's needs particularly well, while the poor buy is a policy that does not meet its needs.

CONCLUSION

This initial article in a series of three has presented some basic information about health insurance in general. The emphasis has been mainly on fundamental principles which contribute to insight into the subject rather than on technical aspects. The two articles to follow will furnish specific information on the various types of health insurance protection and on the contribution each is making toward easing the financial burdens of chronic illness.

In this article, more attention has been given to the insurance companies' approach to health insurance than to the approach used by Blue Cross-Blue Shield and by the independent plans. However, it may be emphasized in conclusion that each of the three approaches has its advantages. American consumers are consequently fortunate in that the differing types of protection, which result from the different approaches, are so widely available.

Moreover, there is much reason to hope that out of the competition of the various insuring organizations of different types may come better policies and plans than any now available. Certainly the growth of health insurance and its increased public acceptance have stemmed largely from competitive factors, and the force of competition has been largely responsible for the increasing extent to which health insurance offers financial protection against chronic illness.

PROGNOSIS IN BRONCHIAL ASTHMA

A Study of the Mortality Among Patients Discharged During the Years 1917-1936 From the Ullevål Hospital (Oslo City Hospital)

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ACCEPTABLE studies of the prognosis of bronchial asthma in adults are rare. The reason is easily understood. Bronchial asthma occurs in different age groups, and admission to the hospital may take place at any stage of the disease. It is possible in the analysis to allow for the age of the patient and the duration of the disease, but in practice the size of the material usually restricts severely the possibilities of grouping. When we try to group the cases according to etiology or the clinical picture, we find that it is almost impossible to reach a satisfactory solution, partly because of our lack of fundamental knowledge of the disease, partly because hospital records are usually incomplete. Of equal importance, however, is the fact that only an unknown percentage of all patients with bronchial asthma is admitted to the hospital. The prognosis for those patients who are never hospitalized may be quite different, possibly better, than for patients treated in the hospital. The prognosis for hospitalized patients may perhaps be looked upon only as a limit in the unfavorable direction of the prognosis for all patients in a community who contract asthma.

American life insurance practice has yielded statistics[1,2] where the number of observation years is quite considerable, but where the diagnostic criteria are likely to be even less well defined than in the material of a large general hospital. Also, insurance applicants are probably as biased a sample of all asthma patients as are the patients of a general hospital, even if the selection is of quite another type. In a study by Dublin and Marks,[3] however, life insurance material has been utilized so as to give the prognosis for relatively well-defined groups which are of interest also to the clinician. For instance, applicants for life insurance who have been free from attack for at least one year prior to the time of application, and with no unfavorable findings at the medical examination, seem to have a mortality which is practically normal.

The purpose of the present investigation was to utilize, if possible, the clinical material of a large general hospital in a study of the mortality of asthma patients. Attempts have been made to contrast groups which might be expected to have a different prognosis. The work has been made difficult by the limited amount of information available in the older records.

MATERIAL AND METHODS

Because of the small number of asthma patients who are discharged each year, it was necessary to include in the material patients from many calendar years. At the same time it was important to get as long a period of observation as possible. Diagnostic indexes are available at all three medical departments at the Ullevål Hospital from the year 1917 onward. The investigation therefore comprises patients who were discharged from one of these departments during the period 1917-1936 with the diagnoses of bronchial asthma, asthma, or asthmatic bronchitis. In all, 411 such individuals were located in the diagnostic indexes from this period. The records for 6 of these patients could not be located in the files. Furthermore, it was decided to exclude 12 patients who had also been hospitalized at the Ullevål Hospital for asthma prior to 1917. The records for the remaining 393 patients were studied independently by two physicians who extracted in code the information on a number of specific points, such as the occurrence or not of a description of a definite attack of dyspnea in the history, the calendar year of first attack, the condition prior to first attack, and the condition at time of discharge from the hospital. The opinions of the two physicians were correlated for each of the items extracted. The results will not be given here,* but the discrepancy was moderate, particularly in view of the general weakness of the material.

It was decided to limit the follow-up to patients who, in the opinion of at least one of the two physicians, had had a definite *attack* of dyspnea. Thirty-eight patients were found not to fulfill this condition. Another 10 patients had died during their first stay in the hospital and were accordingly excluded. Table I shows the remaining 345 patients, distributed according to sex and type of discharge diagnosis.

TABLE I. PATIENTS INCLUDED IN THE FOLLOW-UP, BY SEX AND TYPE OF ASTHMA DIAGNOSIS AT DISCHARGE

	MALES	FEMALES	BOTH SEXES
Main diagnosis:			
Bronchial asthma	122	143	265
Asthma	11	21	32
Asthmatic bronchitis	17	14	31
Subsidiary diagnosis:			
Bronchial asthma	9	4	13
Asthma	1	3	4
All types of diagnosis	160	185	345

During the analysis of the material, males and females have been treated separately throughout.

About 77 per cent of the patients had "bronchial asthma" as the main discharge diagnosis. The number of patients who had been labeled "asthma"

*An unpublished, more detailed report (in Norwegian) is available on request.

and "asthmatic bronchitis" is so limited that a separate presentation of their mortality is not meaningful. There was no significant difference in the prognosis of the various diagnostic groups, and they are all included in the following tabulations.

Table II shows the distribution by sex, age at time of discharge, and calendar year of discharge, of the same patients as in Table I.

TABLE II. PATIENTS INCLUDED IN THE FOLLOW-UP, BY SEX, AGE AT DISCHARGE, AND CALENDAR YEAR OF DISCHARGE

AGE AT DISCHARGE	YEAR OF DISCHARGE						
	1917–1928		1929–1936		1917–1936		
	M	F	M	F	M	F	M + F
0– 9	6	1	6	3	12	4	16
10–19	8	9	6	0	14	9	23
20–29	9	11	8	17	17	28	45
30–39	17	10	20	17	37	27	64
40–49	13	19	17	15	30	34	64
50–59	9	16	13	29	22	45	67
60–69	11	10	8	19	19	29	48
70–79	1	5	7	4	8	9	17
80–89	1	0	0	0	1	0	1
All ages	75	81	85	104	160	185	345

In the follow-up we tried simply to ascertain whether or not the patient was alive on July 1, 1953. If the patient was found to be dead prior to that date, we made notes of the date and place of death. The search was made through various channels, but mainly through the official population registers. The results of the follow-up appear in Table III.

TABLE III. RESULTS OF FOLLOW-UP

	MALES	FEMALES	BOTH SEXES
Died prior to July 1, 1953	82	101	183
Alive on July 1, 1953	70	74	144
Lost from observation	8	10	18
Total	160	185	345

Information as to the status on July 1, 1953, was secured for 327 (94.8 per cent) of the 345 patients who were included in the follow-up.

For the patients who had died an attempt was made to locate the death certificates in the files of the Statistical Central Bureau and the Oslo Health Department. In 10 cases, or 5.5 per cent of all deaths, the certificate could not be found. Three of these patients died in other countries.

The main cause of death for each patient is shown in Table IV.

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TABLE IV. MAIN CAUSE OF DEATH, BY AGE AT DEATH

CAUSE OF DEATH	MALES (AGE AT DEATH)			FEMALES (AGE AT DEATH)		
	BELOW 50	50 AND OVER	ALL AGES	BELOW 50	50 AND OVER	ALL AGES
Asthma (bronchial)	4	13	17	7	17	24
Pneumonia, bronchitis	3	7	10	1	12	13
"Cor pulmonale"	—	—	—	—	2	2
Various designations of myocardial disease	7	14	21	2	16	18
Heart paralysis, sudden death, pulmonary embolus	2	1	3	1	2	3
Arteriosclerosis	—	2	2	—	2	2
Cerebral vascular attack	—	1	1	1	5	6
Malignant tumors	4	3	7	—	6	6
Tuberculosis	2	1	3	2	—	2
Diabetes	—	1	1	—	—	—
Diseases of the urinary system, uremia	—	6	6	1	5	6
Gastrointestinal diseases, and diseases of the liver	—	2	2	1	4	5
Other specified diseases	1	2	3	—	1	1
Senility	—	—	—	—	3	3
Accidents and suicides	1	2	3	1	2	3
Death certificate not located	1	2	3	2	5	7
Total number of deaths	25	57	82	19	82	101

Most of the 18 patients who were lost from observation had been observed for some time after discharge from the hospital. The age and sex distribution for these patients showed no striking features, but, as one would expect, a relatively large proportion belonged to the first part of the twenty-year period. It is not possible to say whether patients who are lost from observation have a prognosis which is better or worse than the average. In view of the fact, however, that these patients constitute only about 5 per cent of the material, peculiarities in their prognosis cannot be of any consequence for the results.

For patients who were alive on July 1, 1953, or who were lost from observation prior to that time, the number of observation years is counted as the difference between 1953, or the year of last observation, and the calendar year of discharge. For patients who have died the number of observation years is counted as the number of completed years after discharge plus ½.

The total number of observation years in the material is 2,582.0 for males and 2,660.5 for females.

We have measured the mortality of the asthma patients by calculating the ratio between actual and expected number of deaths in various subgroups of the material. This ratio will be referred to as the mortality ratio. Expected number of deaths has been obtained by multiplying the number of observation years with the death rate (m_x) of a corresponding age-sex-calendar year group in a reference table.

As a reference we have used the mortality in Oslo, calculated ad hoc from official data giving the size of the population and number of deaths in each

calendar year. The raw data were available in 10-year age groups, but the death rates were calculated by linear interpolation for 5-year age intervals.

In addition to the Oslo mortality we have used the official death rates for the whole of Norway as a standard of comparison in Tables V and VI.

TABLE V. MORTALITY BY AGE, IRRESPECTIVE OF NUMBER OF YEARS AFTER DISCHARGE

AGE	NUMBER OF OBSERVATION YEARS	D	E_O	E_B	D/E_O	D/E_B
			Males			
–29	533.5	3	1.39	1.92	2.2	1.6
30–39	464.5	5	2.37	2.29	2.1	2.2
40–49	600.0	16	5.02	3.64	3.2	4.4
50–59	509.5	19	7.95	5.31	2.4	3.6
60–69	311.5	23	10.45	7.19	2.2	3.2
70–79	146.0	14	10.56	8.12	1.3	1.7
80–	17.0	2	2.90	2.90	0.7	0.7
All ages	2,582.0	82	40.64	31.37	2.0	2.6
			Females			
–29	348.0	4	0.89	1.17	4.5	3.4
30–39	428.5	5	1.28	1.43	3.9	3.5
40–49	524.0	10	2.53	2.37	4.0	4.2
50–59	588.0	18	5.80	4.96	3.1	3.6
60–69	513.5	31	11.90	9.65	2.6	3.2
70–79	235.0	26	13.94	11.65	1.9	2.2
80–	23.5	7	3.50	3.75	2.0	1.9
All ages	2,660.5	101	39.84	34.98	2.5	2.9

D: Actual deaths.
E_O: Deaths expected on basis of the Oslo mortality.
E_B: Deaths expected on basis of the mortality in Norway.

RESULTS

In Table V the material is grouped according to age attained, irrespective of the number of years after discharge and irrespective of the duration from first attack until discharge.

We find a considerable excess mortality for both males and females. For all ages the actual number of deaths for males is about twice the number expected on the basis of the Oslo mortality in the period covered by the study. The corresponding figure for females is 2.5.

The mortality ratios are somewhat irregular at ages below 50. For ages 50 and above there is in both sexes a steadily declining mortality ratio with advancing age.

Table VI shows the mortality ratios for various 5-year periods after discharge for all ages combined.

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TABLE VI. MORTALITY AT DIFFERENT PERIODS OF TIME AFTER DISCHARGE, ALL AGES

NUMBER OF YEARS AFTER DISCHARGE	NUMBER OF OBSERVATION YEARS	D	E_O	E_B	D/E_O	D/E_B
			Males			
0– 4	711.5	23	11.43	8.42	2.0	2.7
5– 9	597.0	20	11.64	9.18	1.7	2.2
10–14	489.5	17	8.01	6.32	2.1	2.7
15–19	401.5	13	7.30	6.55	1.8	2.0
20–	382.5	9	7.44	5.80	1.2	1.6
Total	2,582.0	82	45.82	36.27	1.8	2.3
			Females			
0– 4	774.0	42	10.89	9.01	3.9	4.7
5– 9	592.5	25	8.55	7.52	2.9	3.3
10–14	512.0	12	7.63	6.42	1.6	1.9
15–19	418.0	10	7.81	7.98	1.3	1.3
20–	364.0	12	9.11	8.45	1.3	1.4
Total	2,660.5	101	43.99	39.38	2.3	2.6

D: Actual deaths.
E_O: Deaths expected on basis of the Oslo mortality.
E_B: Deaths expected on basis of the mortality in Norway.

The total number of deaths expected on the basis of the Oslo mortality is given in Table VI as 45.82 for males and 43.99 for females. The corresponding figures in Table V were 40.64 and 39.84. This discrepancy is due mainly to the fact that 10-year age groups have been used in the calculation of expected number of deaths in Table VI (and Tables VII to XIII), with the underlying assumption that the average age in the 10-year group falls in the middle of the group. This assumption does not always hold, particularly in the higher age groups, where the average age is closer to the lower limit of the group. Table V, therefore, calculated on the basis of 5-year age groups, gives a more correct expression of the total excess mortality in the material than does Table VI.

The error in the expected number of deaths in Tables VI to XIII is limited almost exclusively to age 60 years and above at time of discharge. The implications of this error were studied carefully, but were found to be of no consequence for the conclusions drawn in the following.

The mortality ratio (Table VI) for females is considerably larger for the first ten years after discharge than in later years. For males we find no distinct reduction of the mortality ratio with increasing number of years after discharge. It is necessary at this point, however, to take into account calendar year of discharge, age, and duration of illness at time of discharge. Unfortunately, the material is so small that it has been necessary to use a very coarse grouping when studying the interaction of these variables.

TABLE VII. MORTALITY FOR PATIENTS DISCHARGED DURING THE TWO CALENDAR-YEAR PERIODS 1917-1928 AND 1929-1936 IN VARIOUS FIVE-YEAR PERIODS AFTER DISCHARGE. ALL AGES COMBINED

NUMBER OF YEARS AFTER DISCHARGE	YEARS OF DISCHARGE							
	1917–1928				1929–1936			
	NUMBER OF OBSERVATION YEARS	D	E_O	D/E_O	NUMBER OF OBSERVATION YEARS	D	E_O	D/E_O
Males								
0– 4	322.0	14	4.67	3.0	389.5	9	6.76	1.3
5– 9	274.0	6	4.38	1.4	323.0	14	7.26	1.9
10–14	231.0	8	2.84	2.8	258.5	9	5.17	1.7
15–19	193.0	6	2.83	2.1	208.5	7	4.47	1.6
20–	316.5	7	5.99	1.2	66.0	2	1.45	1.4
Total	1,336.5	41	20.71	2.0	1,245.5	41	25.11	1.6
Females								
0– 4	329.5	15	5.03	3.0	444.5	27	5.86	4.6
5– 9	250.0	14	3.72	3.8	342.5	11	4.83	2.3
10–14	214.0	2	3.14	0.6	298.0	10	4.49	2.2
15–19	197.5	5	3.84	1.3	220.5	5	3.97	1.3
20–	306.0	10	7.95	1.3	58.0	2	1.16	1.7
Total	1,297.0	46	23.68	1.9	1,363.5	55	20.31	2.7

D: Actual deaths.
E_O: Deaths expected on basis of the Oslo mortality.

Table VII compares the prognosis for patients discharged in 1917 to 1928 with the prognosis for those discharged in 1929 to 1936. The mortality ratio for females in the second period is considerably larger than in the first period. However, the direction of the difference is not the same in the two sexes, and within each sex the sign of the difference varies with varying number of years after discharge. In what follows, we have disregarded the calendar year of discharge.

The other factors mentioned above are correlated in Tables VIII to X. Duration of illness at time of discharge has been counted as the difference between calendar year of discharge and calendar year of first attack. The numbers are small everywhere, but it seems reasonable to draw the following conclusions:

Neither males nor females show a simple association between *duration at time of discharge* and the prognosis after discharge. Table VIII shows, however, that asthma patients with a short duration of illness have their highest mortality ratio during the first five years after discharge, while patients who had had their attacks for ten years or more, showed a mortality ratio approximately equal for all years after discharge. If observation were to be continued in the

TABLE VIII. MORTALITY RATIOS CALCULATED ON BASIS OF OSLO MORTALITY. MATERIAL DISTRIBUTED ACCORDING TO DURATION OF ILLNESS AT TIME OF DISCHARGE AND NUMBER OF YEARS AFTER DISCHARGE

DURATION OF ILLNESS (IN YEARS) AT TIME OF DISCHARGE	NUMBER OF YEARS AFTER DISCHARGE			TOTAL
	0–4	5–14	15–	
Males				
0–1	2.9 (10)	1.8 (11)	1.3 (7)	1.9 (28)
2–9	2.1 (7)	1.8 (10)	0.9 (4)	1.6 (21)
10–	1.6 (3)	3.6 (12)	2.3 (5)	2.7 (20)
Unknown	1.1 (3)	0.8 (4)	2.2 (6)	1.3 (13)
Total	2.0 (23)	1.9 (37)	1.5 (22)	1.8 (82)
Females				
0–1	4.6 (16)	1.6 (11)	1.2 (11)	2.0 (38)
2–9	5.4 (12)	2.3 (7)	1.2 (3)	2.8 (22)
10–	2.7 (6)	2.5 (8)	2.9 (7)	2.7 (21)
Unknown	2.7 (8)	3.4 (11)	0.3 (1)	2.1 (20)
Total	3.9 (42)	2.3 (37)	1.3 (22)	2.3 (101)

In parentheses: Actual deaths.

TABLE IX. MORTALITY RATIOS CALCULATED ON BASIS OF OSLO MORTALITY. MATERIAL DISTRIBUTED ACCORDING TO DURATION OF ILLNESS AT TIME OF DISCHARGE AND AGE AT DISCHARGE

DURATION OF ILLNESS (IN YEARS) AT TIME OF DISCHARGE	AGE AT DISCHARGE			ALL AGES
	0–29	30–59	60–	
Males				
0–1	3.9 (5)	1.7 (16)	1.6 (7)	1.9 (28)
2–9	2.5 (3)	1.2 (8)	1.8 (10)	1.6 (21)
10–	1.9 (1)	3.5 (18)	0.5 (1)	2.7 (20)
Unknown	5.2 (3)	1.2 (5)	0.9 (5)	1.3 (13)
Total	3.4 (12)	1.9 (47)	1.3 (23)	1.8 (82)
Females				
0–1	3.8 (3)	2.1 (26)	1.6 (9)	2.0 (38)
2–9	4.5 (3)	2.4 (12)	3.2 (7)	2.8 (22)
10–	3.2 (1)	2.5 (12)	2.8 (8)	2.7 (21)
Unknown	3.1 (2)	1.1 (6)	3.5 (12)	2.1 (20)
Total	3.8 (9)	2.0 (56)	2.5 (36)	2.3 (101)

In parentheses: Actual deaths.

future, one would then expect to find an almost normal death rate among patients who were discharged only a few years after their first attack, in contrast to the group with a duration of illness of ten years or more, where one would expect to find an excess mortality in the future also. Subdivision according to *age at discharge* (Table IX) shows the largest mortality ratio in the group 0-29 both for males and females, but expected numbers of deaths are so small that random variation may have caused the difference. If we study the variation of the mortality ratio with age within the various duration groups, or within the various groups of years after discharge (Table X), we find no evidence of an interaction between age and the factors mentioned. When we consider the association between the mortality ratio and *number of years after discharge*, we find for females that in each age group the mortality ratio drops off with increasing number of years after discharge. This tendency seems to be outside the range of chance variation. For males, however, the trend is not consistent from age group to age group.

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TABLE X. MORTALITY RATIOS CALCULATED ON BASIS OF OSLO MORTALITY. MATERIAL DISTRIBUTED ACCORDING TO AGE AT DISCHARGE AND NUMBER OF YEARS AFTER DISCHARGE

AGE AT DISCHARGE	NUMBER OF YEARS AFTER DISCHARGE			TOTAL
	0–4	5–14	15–	
		Males		
0–29	3.2 (2)	2.4 (3)	4.2 (7)	3.4 (12)
30–59	2.0 (9)	2.6 (24)	1.2 (14)	1.9 (47)
60–	1.9 (12)	1.1 (10)	0.5 (1)	1.3 (23)
All ages	2.0 (23)	1.9 (37)	1.5 (22)	1.8 (82)
		Females		
0–29	5.8 (3)	4.5 (4)	2.0 (2)	3.8 (9)
30–59	5.0 (20)	2.0 (18)	1.3 (18)	2.0 (56)
60–	3.0 (19)	2.4 (15)	1.3 (2)	2.5 (36)
All ages	3.9 (42)	2.3 (37)	1.3 (22)	2.3 (101)

In parentheses: Actual deaths.

The prognosis has been studied in relation to the *condition at discharge*, to the extent that it was possible to evaluate this factor on basis of the records. Table XI compares two groups:

Patients with a pathologic condition at discharge: definite or doubtful sign of cardiovascular disease, bronchiectasis, emphysema, or "other condition of prognostic significance."

Patients without a pathologic condition at discharge.

We find that for males the difference in mortality ratio between the two groups is very small. A closer scrutiny of the two groups showed that the average age was considerably higher in the group with pathologic conditions.

TABLE XI. MORTALITY ACCORDING TO CONDITION AT DISCHARGE IN VARIOUS FIVE-YEAR PERIODS AFTER DISCHARGE; ALL AGES COMBINED

NUMBER OF YEARS AFTER DISCHARGE	AT DISCHARGE					
	PATHOLOGIC FINDINGS			NO PATHOLOGIC FINDINGS		
	D	E_O	D/E_O	D	E_O	D/E_O
Males						
0– 4	18	7.79	2.3	5	3.66	1.4
5– 9	13	7.47	1.7	7	4.16	1.7
10–14	11	4.19	2.6	6	3.81	1.6
15–19	5	3.56	1.4	8	3.73	2.1
20–	4	3.96	1.0	5	3.48	1.4
Total	51	26.97	1.9	31	18.84	1.6
Females						
0– 4	26	6.78	3.8	16	4.11	3.9
5– 9	20	4.12	4.9	5	4.44	1.1
10–14	6	2.79	2.2	6	4.85	1.2
15–19	3	2.90	1.0	7	4.89	1.4
20–	2	1.73	1.2	10	7.39	1.4
Total	57	18.32	3.1	44	25.68	1.7

D: Actual deaths.
E_O: Deaths expected on basis of the Oslo mortality.

Table IX showed that the mortality ratio in the whole material was largest in the youngest age group. The ratios in Table XI were therefore adjusted for age, which resulted in the figures in Table XII. The adjustment has increased the difference between the two groups for males, while the female figures have remained uanaltered.

TABLE XII. MORTALITY RATIOS FOR THE TWO GROUPS OF TABLE XI, ADJUSTED FOR THE AGE DIFFERENCE BETWEEN THE GROUPS

	PATHOLOGIC FINDINGS	NO PATHOLOGIC FINDINGS
Males, all years after discharge	2.0	1.5
Females, all years after discharge	3.1	1.7

A subgroup of the patients with no pathologic condition at time of discharge was studied separately, namely, those with a duration of illness of 0 or 1 year, and with no previous hospitalization. Even in this very select group

the death rate was about 50 per cent higher than in the Oslo population. The material was very small, however: 31 males and 38 females in all, with 10 and 19 actual deaths, respectively.

The information in the records on the *condition prior to first attack* has been utilized to define the four groups compared in Table XIII.

1. Patients who prior to first attack had definite or doubtful cardiovascular disease or some other disease of prognostic significance.
2. Patients who prior to first attack had chronic bronchitis, or who developed their first attack on the basis of a preceding upper respiratory infection.
3. Patients with doubtful bronchitis or upper respiratory infection prior to first attack.
4. Patients without any pathologic condition prior to first attack.

In Table XIII we note that males in the first group did not have a particularly poor prognosis. This result is analogous to that obtained in the analysis of the prognosis according to condition at discharge from hospital. For females, however, the mortality ratio is considerably larger in the first group than in any of the others. It is surprising that the prognosis in this investigation did not appear to depend on whether the attack developed on the basis of chronic bronchitis (upper respiratory infection). The number of patients with no pathologic condition however, is small.

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TABLE XIII. MORTALITY RATIOS CALCULATED ON BASIS OF OSLO MORTALITY. MATERIAL DISTRIBUTED IN FOUR GROUPS CHARACTERIZED BY CONDITION PRIOR TO FIRST ATTACK

CONDITION PRIOR TO FIRST ATTACK*	MALES		FEMALES	
Cardiovascular disease or other prognostically significant condition	1.9	(22)	4.2	(27)
"Chronic bronchitis"	1.9	(32)	1.8	(41)
"Doubtful chronic bronchitis"	1.6	(23)	2.5	(23)
No pathologic condition	1.4	(5)	2.0	(10)
Total	1.8	(82)	2.3	(101)

In parentheses: Actual deaths.
*See text for definition.

SUMMARY

A total of 411 patients were discharged from the three medical departments at the Ullevål Hospital with the diagnoses of bronchial asthma, asthma, or asthmatic bronchitis, during the years 1917 to 1936.

Of these, 66 were eliminated from the present study because of one of the following causes: (a) The patient died during his first stay in hospital (10). (b) The record could not be located (6). (c) The patient had also been hospitalized at the Ullevål Hospital for asthma prior to 1917 (12). (d) The record did not contain a description of a definite attack of dyspnea at any time (38).

Of the remaining 345 patients, 327 were followed until death or until July 1, 1953. One hundred and forty-four were alive on July 1, 1953, while 183 were

dead prior to that date. The actual number of deaths for males was about twice the number expected on the basis of the Oslo mortality in the same period. For females the corresponding number was 2.5.

The mortality ratio did not differ appreciably for patients discharged in the two calendar-year periods 1917-1928 and 1929-1936.

The mortality ratio for females was largest during the first five years after discharge, and thereafter dropped off. For males there was no definite trend in this direction.

Patients in the age group 0-29 at discharge had a larger mortality ratio than older patients, but actual deaths were few and the result is therefore somewhat uncertain.

Patients with various durations of illness at time of discharge showed about the same mortality ratio when all years after discharge were considered simultaneously. Patients with short duration at time of discharge had their highest mortality ratio during the first five years after discharge, while patients with at least ten years' duration had a mortality ratio approximately equal in all years after discharge.

Patients whose records contained a description of cardiovascular disease, bronchiectasis, emphysema, or other conditions of prognostic significance at time of discharge from the hospital, had a mortality ratio that was only moderately higher than patients whose records did not indicate such conditions.

The prognosis for patients who developed their first attack of dyspnea on the basis of chronic bronchitis or a preceding respiratory infection did not differ significantly from the prognosis of patients with no pathologic condition prior to first attack.

We are indebted to Anette Brochmann, M.D., for her cooperation in extracting information from the records.

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Review

THE ROLE OF CONGENITAL ANOMALIES IN THE ETIOLOGY OF CHRONIC DISEASES

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IN THE Announcement of this JOURNAL[147] it was emphasized that a need exists for longitudinal studies of the natural history of chronic diseases, that children as well as adults are victims of protracted illness and that the long-range approach to chronic disease must be preventive. The present review was written with these postulates in mind. It is the purpose of the following pages to attract attention to prenatal factors in the etiology of chronic diseases and to stress the need for reorientation in the research concerned with the prevention of a large section of chronic disturbances.

Under congenital anomalies we understand anomalies present at birth. Such anomalies may be structural (malformations) or metabolic. Malformations may be macroscopic or microscopic. They may be genetically determined and hereditary or they may be due to environmental interference during embryonic or fetal life. Congenital anomalies may cause disease from the time of birth or become a source of illness in later life.

Many of the anomalies to be discussed are well recognized as prenatal disorders. Others are often dealt with together with disorders of postnatal origin, so that sight is lost of their etiological pecularities. Medical specialties are organized to treat, but not to prevent diseases; they are to a great extent divided by anatomic borderlines and classified according to organ systems; dermatology, internal medicine, endocrinology, gynecology, urology, gastroenterology, ophthalmology, orthopedics, hematology, and others are the products of modern medical specialization. It is a peculiarity of prenatal disorders that they do not respect the borders of anatomic organs nor the limits of established specialties. Many disorders of prenatal origin affect several systems of the body, and patients as well as specialists are baffled by the protean manifestations of some of these syndromes. Specialists unable to treat all the symptoms of patients with multiple anomalies refer such persons to other specialists, who also can treat only one phase of the disorder. To excuse the failure of finding a central focus for the

multiplicity of symptoms such patients may be labeled as "degenerated," "constitutionally or genetically inferior," "psychopathic," or "endocrine," according to the point of view of the examiner.

The plight of such patients may be illustrated by the example of a syndrome of multiple anomalies, such as *arachnodactyly* (Marfan's syndrome). Children born with this syndrome are long and thin, have an "old and sad" face, and strikingly long fingers and toes. As they grow older they are confronted with many orthopedic problems. Contractures and dislocation of joints, genu valgum, pes equinus or planus, and hammertoes may be present. Seventy-five per cent of the patients have congenital malformations of the eye such as dislocation of the lens, cataract, buphthalmos, megalocornea, defects of the iris, coloboma, or others. Cardiovascular disease is observed in about 20 per cent of the patients. There may be interauricular septal defects, malformations of the aorta, valvular defects, and cystic medionecrosis of the aorta[10] leading to dissecting aneurysm. The lungs often show abnormal lobe formations and diffuse cystic changes. Malformations of the intestinal tract have been observed. There are also such endocrine disturbances as retarded sexual development, cryptorchidism, cysts of the ovary, or hypoplasia of the uterus.[169] To obtain adequate medical treatment, such patients need the help of many specialists. They go from the pediatrician to the orthopedic surgeon and to the ophthalmologist. As they grow older they seek aid from a cardiologist, a lung specialist, a gastroenterologist and possibly an endocrinologist. It surprises no one that they finally consult a psychiatrist; paranoia and suicide have actually occurred in several of these unfortunate patients. True, arachnodactyly is a rare syndrome, but there are many other disease pictures of multiple congenital malformations, many of them neither named nor recognized, and their sum total is responsible for a large part of chronic illness. Arachnodactyly represents an example of multiple disorders which were labeled by older clinicians "heredodegenerative" and are now attributed to a "pleiotropic gene."

It must not be assumed, however, that all syndromes of multiple anomalies are hereditary. It has been recognized,[90] for instance, that a syndrome of congenital heart disease, cataract, deafness, and mental deficiency may result from an accidental prenatal infection, rubella. Although our knowledge of such environmental factors causing multiple anomalies in man is still limited, experimental work of recent years has demonstrated that such syndromes can be produced by a variety of environmental factors.[207] The multiplicity of congenital anomalies points to an early causation of the patient's difficulties, but it does not necessarily indicate that they are hereditary. It will be shown later that the demonstration of the multiple origins of congenital syndromes is of fundamental importance not only to the patient and his family but also to the trend of investigation in this field. We should consider congenital anomalies as the result of prenatal disorders, which may be of genetic or of environmental origin, or both.

It has been recognized in recent years that malformations known as clinical entities may be of differing origins. A hereditary congenital malformation such as microcephaly or cataract may be simulated by malformations caused by prenatal diseases. The nonhereditary malformation is now called a "phenocopy"

according to a term introduced into physiologic genetics by Goldschmidt.[88] This differentiation could be extended to histologic or metabolic malformations. There are hereditary thrombopenias[181] which have nonhereditary phenocopies. There exists a form of agammaglobulinemia which is genetically determined,[32] and there are forms which are acquired. The fact that a clinical entity appears to be hereditary in some pedigrees does not permit the conclusion that the disorder is always of the same etiology. In some clinical entities the hereditary forms prevail, in others the acquired are more frequent.

Many fertilized ova are defective because of faulty genetic endowment or because of postconceptional injuries. During intrauterine life the developing embryos undergo a screening process which eliminates the most defective organisms. This intrauterine process of natural selection leads to premature death of the most deformed or diseased fetuses, resulting in miscarriage, abortion, or stillbirth. Embryos and fetuses with lesser defects can live through the intrauterine period and reach the end of gestation. Then a new screening process begins which selects survivors according to different principles, since intrauterine and extrauterine requirements for life differ greatly. Congenital anomalies interfering with postnatal life contribute considerably to neonatal mortality. Thus many neonatal deaths are due to prenatal pathologic factors and it is not surprising that hygienic and medical procedures which prove successful in the reduction of the mortality of older infants and children are not capable of reducing neonatal mortality to the same extent. Natural selection proceeds throughout postnatal life and contributes to many diseases of children and adults. Stockard[185] contended: "One may go far in defense of the thesis that the human personality finally dies from some defect, 'weak spot,' that was present at birth. In other words, the individual dies of a disease (faulty construction) with which he was born." However, with increasing age *postnatal* injurious factors assume increasing importance in human morbidity. The point of view expressed by Stockard is, therefore, most appreciated by physicians dealing with the younger age groups, the pediatricians. The role of congenital anomalies in human diseases is most obvious in pediatric practice, and I shall select most of the examples illustrating the role of prenatal factors in chronic diseases from the pathology of children. However, many children suffering from such chronic disorders survive to adulthood and sometimes defects determined in prenatal life lead to overt disease in older persons only. Postnatal injurious factors such as traumas, infections, or toxins tolerated by the normal organism may become pathogenic for an organism with an inherent weakness. Thus prenatal and postnatal factors often combine to bring about disease.

In recent years impressive progress has been made in the treatment of infectious diseases, but it has also been found that some patients do not respond to the new remedies or show a relapse soon after temporary improvement. At the same time, progress has been made in the understanding of many types of inherent weakness. Structural and chemical anomalies of prenatal origin are being recognized in increasing numbers as the basic defect of many diseases. Thus "constitutional inferiorities" and "degenerative tendencies," long postulated in the explanation of differential susceptibility to disease, are becoming better defined and understood, if prenatal pathogenic factors are taken into consideration.

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In the following pages examples will be cited to illustrate this point. Whenever possible an attempt will be made to give quantitative estimates of the contributions made by congenital anomalies to the groups of chronic diseases under consideration. Such figures are necessarily open to criticism, particularly if the disorder under discussion is brought on by a combination of prenatal and postnatal factors. Different observers may classify the same disease differently according to their personal concept of the importance of the etiologic factors involved. In addition, perceptible shifts are taking place in many fields of pathology, owing to elimination of postnatal, and persistence of prenatal, pathogenic factors. For instance, blindness or deafness due to infections are being steadily reduced by the use of antibiotics, while cases of prenatal origin assume increasing relative importance.

MENTAL DEFICIENCY

Conservative estimates place the incidence of mental deficiency at 1 per cent. There are more than a million and a half mental defectives in the United States.[191] It is difficult to evaluate the etiologic factors responsible for mentally defective persons at large; but it is possible to obtain such information in institutions, where patients and their families can be investigated. Yannet[226] found that in over 90 per cent of 2,000 patients admitted to the Southbury Training School, the deficiency could be attributed to etiologic agents operative during the prenatal period. In only 3 per cent could injuries during birth be implicated, and in 6 per cent postnatal factors such as infections or trauma. In a study of the neuropathology of 543 autopsied mental defectives, Malamud[136] classified 400 (74 per cent) of the brains examined as congenitally malformed.

Definite progress has been made in the etiologic analysis and classification of mental disorders of prenatal origin. The differentiation of primary (idiopathic, endogenous) and secondary (extrinsic, exogenous) amentia is hardly tenable. It has been thought that primary aments could be recognized by "stigmata of degeneracy," i.e., associated somatic malformations, while secondary aments are essentially "well formed and often comely in appearance."[195] The assumption that only a defective gene can produce syndromes of mental *and* somatic anomalies, i.e., "stigmata of degeneracy," has been disproved. It is now well recognized that prenatal infections such as rubella or toxoplasmosis can result in mental deficiency accompanied by congenital malformations such as cataract, heart defects, microcephaly, and others. Such "stigmata of degeneracy" are, therefore, not characteristic of germ plasma changes. On the other hand, it was learned that well-formed, even beautiful, children may be mentally defective because of an inherited metabolic disturbance such as phenylketonuria. This change of our knowledge is of practical importance, since a diagnosis of primary amentia implying a hereditary defect stigmatizes not only the defective child but also his family. It is of theoretical importance because it does away with superficial labels which impeded progress in etiologic research.

These remarks must not be interpreted as an underestimation of the role played by genetic factors in the causation of mental defects. On the contrary, the exclusion of disorders of environmental origin from the mass of hereditary syn-

dromes will benefit genetic investigations. How can Mendelian inheritance be demonstrated in a hodge-podge of etiologic entities? Those who pay attention to genetic factors only, and try to explain all congenital anomalies by simple Mendelian inheritance, do a poor service to the science of genetics. It is estimated that genetic factors are responsible for about one-half of the cases of congenital mental deficiency.[225]

Further progress is being made by classification of defectives according to anatomic and functional anomalies which accompany the mental defects. The disease picture of *mongolism* is well known. By observation of a number of somatic characteristics an experienced physician can diagnose a typical case at birth and predict the limitations of the child's development. Little is known about the causation of this disorder except that increasing maternal age plays an etiologic role. *Sporadic cretinism* due to congenital aplasia of the thyroid gland is a rare but well-defined disorder. By thyroid substitution therapy the mental development can be ameliorated to a certain extent. *Endemic cretinism*, once a widespread form of mental deficiency, is hardly seen in the United States at the present time. This disorder can be attributed to maternal nutritional deficiencies and prevented by an adequate iodine intake of the mother. In mountainous areas of Europe tens of thousands of cases of mental deficiency proved preventable by a simple environmental procedure such as distribution of iodized salt.

The role of *prenatal infections* such as rubella and toxoplasmosis in the origin of mental deficiency has been mentioned. Although these known infections do not account for many cases of mental deficiency, they are of great theoretical interest. It is important that a *subclinical* infection of the mother may cause severe damage to the embryo or fetus.[207] This fact opens new vistas to etiologic investigations.

It has been recognized that in at least one disorder the "stigma of degeneracy" may be the *cause* of the mental deficiency: *craniostenosis* due to premature fusion of the cranial bones interfers with the normal growth of the brain and leads to mental defects and symptoms of increased intracranial pressure. The creation of artificial sutures can relieve many of the postnatal complications and improve the mental development.

A tendency to formation of multiple tumors can be transmitted from one generation to another. Such disorders named "phacomatoses" or "hamartoses" represent inherited tissue anomalies resulting in multiple tumors of the brain, skin, and viscera. *Tuberous sclerosis* is a form of mental deficiency which is due to formation of such tumors of the neuroglia of the brain. The patients suffer frequently from epilepsy and can be recognized externally by adenoma sebaceum, a skin lesion visible on the face. Tumors of the heart and the kidneys may also develop (p. 77). *Recklinghausen's neurofibromatosis* represents a different form of hamartosis in which mental deficiency may occur (p. 77). A syndrome of congenital nevus flammeus of the face combined with vascular nevi of the leptomeninges may result in mental deficiency, epilepsy, and hemiparesis. In this condition, also called *Sturge-Weber syndrome*, heredity has not been proved. The association of mental deficiency with dyskeratoses was thoroughly discussed by Ewing.[67]

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Microcephaly is sometimes, but not always, due to recessive inheritance. A more complicated disorder, the *Laurence-Moon-Biedl syndrome*, is also transmitted as a recessive trait. In this condition mental deficiency is combined with polydactylism, retinitis pigmentosa, obesity, and sexual underdevelopment. Normal parents may have several children of this type and, also, normal children. Polydactylism is the only anomaly of this syndrome recognizable at birth and may thus be in some families an early sign of the sad future of the affected children.

The storage diseases leading to mental deterioration are metabolic disorders and generally inherited as recessive traits. *Familial amaurotic idiocy* develops soon after birth and is lethal within the first few years of life. The pathologic changes and the symptoms are due to a disturbance of the intracellular lipoid metabolism characterized by excessive deposits of phosphatides in the ganglion cells. In the closely related *Niemann-Pick disease*, sphingomyelin deposits are found in the liver, spleen, lymph nodes, bone marrow, and in the central nervous system. In the acute, infantile form of *Gaucher's disease* the mental and physical signs can be traced to abnormal accumulation of the lipoid kerasin in many tissues. Another form of disturbed intracellular metabolism results in *gargoylism*. This disorder is characterized by deposits of abnormal mucoproteids in the cells of many tissues,[187] while lipoid deposits reminiscent of those seen in amaurotic idiocy are seen in the ganglion cells of the brain.[113] Most of the children with this disorder are mentally retarded. They show hepatosplenomegaly, cloudy corneas, and dwarfism. The skeletal anomalies found are of particular interest since they have been classified as atypical chondrodystrophies or chondrodysplasias (p. 60). In this disorder the cerebral changes as well as the osseous "stigmata" can be ascribed to an inborn error of metabolism which results in abnormal intracellular deposits. Other forms of mental and physical deviations may be due to similar metabolic disorders, although no abnormal cellular contents are detectable in the pathologic tissues.

Phenylpyruvic oligophrenia is the best example of an inborn error of metabolism leading to neurological and mental disturbances. Patients with this disorder are unable to convert phenylalanine into tyrosine. Phenylalanine accumulates in the blood and cerebrospinal fluid, and is excreted in the urine either unchanged or as phenylpyruvic acid. The disorder is related to alkaptonuria in which, however, no mental disturbances appear. In phenylketonuria severe mental defects, epilepsy, and neurological disturbances develop. The patients are usually blond and blue-eyed and have a sensitive skin. More than one child of a family may be affected and there is a high frequency of consanguineous marriages among the parents.[74,139,181] An abnormal recessive gene is held responsible for the development of this disorder. Attempts have been made to influence the course of this disease by dietary measures and it has been reported that improvement of the patient's mental status can be achieved by a diet low in phenylalanine.[22,222]

Many other types of mental deficiency have been named and classified but there remains a large group of defectives of the familial type which do not correspond to the disease pictures described. They are usually the offspring of

defective parents and they have siblings with inferior mentality. The mode of inheritance is not clear and it is likely that they cannot be considered a genetic entity. These persons are, as a rule, of moron level and they are not characterized by specific physical anomalies.[225] However, some of them show on autopsy a reduced brain volume and true malformations of the spinal cord.[17]

CENTRAL NERVOUS SYSTEM

Congenital malformations of the central nervous system are very frequent. About one-half of all malformations recognized at birth are cerebrospinal.[168] Spina bifida, anencephaly, and hydrocephaly are the leading anomalies. Many cases of this type are not compatible with life and are eliminated, therefore, as causes of chronic illness. *Spina bifida*, for instance, accounts for 5.7 per cent of crippled children[198] in the age group under 1 year, but only for 1.9 per cent of the age group from 1 to 4 years. This decrease illustrates the postnatal elimination of seriously deformed infants, but milder forms of malformations of the central nervous system persist, causing diverse chronic manifestations. Spina bifida requires surgical operation, orthopedic treatment, urologic attention, and a great deal of nursing care. *Encephaloceles* may be associated with cerebral, nasal, or oral defects.

Minor anomalies of the central nervous system related to spina bifida and encephalocele are relevant in this discussion. *Congenital dermal sinus tracts* present themselves as inconspicuous cutaneous dimples in the occipital region or over the spinal column. If they do not extend beyond the skin they may be entirely harmless. However, pilonidal sinuses and cysts may lead to complications. They are good examples of minor congenital malformations which predispose to repeated and chronic infections after the age of puberty. Dermal sinuses communicating with intraspinal structures may lead to a variety of complications which may present as meningitis or spinal tumor. In less pronounced cases, back pain, fever, paraesthesia, or muscular weakness may be the symptoms elicited. Dermal sinus tracts originating from the scalp are often overlooked since the cutaneous manifestations may be covered by hair. Yet they can be a portal of entrance for infections and lead to meningitis or be indicative of a dermoid cyst or an abscess located in the cranial cavity. Such complications were diagnosed until recently as meningitis or brain tumors, since the congenital nature of the basic disorder was often overlooked.[109]

Hydrocephalus may be caused by a variety of developmental defects. Stenosis of the Sylvian aqueduct, neuroglial septa in the aqueduct, atresia of the foramina of Magendie and Luschka, and the Arnold-Chiari malformation are obvious congenital anomalies[109,170] leading to hydrocephalus. Some of the cerebral tumors resulting in hydrocephaly are also congenital malformations. Rathke-pouch tumors, dermoid cysts, teratomas,[24] pinealomas,[86] hamartomas,[92,170] arteriovenous aneurysms,[48,170] "melanosis,"[72,170] cerebellar angioreticulomas (Lindau tumors)[18] and others[86] are due to developmental errors. It should be emphasized that some of these tumors may cause clinical manifestations many years after birth, although they date back to deviations in embryonic life.

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Hydrocephaly due to prenatal toxoplasmosis may take a protracted course. It is associated with chorioretinitis and cerebral calcifications. A hereditary form of hydrocephaly, genetically related to anencephaly, spina bifida, and encephalocele has been described by Polman.[160] Hydranencephaly, an extreme form of cerebral deficiency and hydrocephaly, is of interest because this severe anomaly may go unrecognized at birth and be compatible with a life span of several years.[95]

Microcephaly due to prenatal arrest of cerebral development results always in severe mental deficiency and sometimes in epilepsy. This anomaly is not an etiologic entity. Exposure of the mother to radiation during pregnancy, prenatal rubella or toxoplasmosis, and heredity have been recognized as etiologic factors.[27]

Agenesis of the corpus callosum leads to a variety of chronic symptoms such as epilepsy, mental deficiency, speech defect, hemiparesis, dyskinesias, lack of coordination, and others. The manifestations become apparent before the age of 2 years in the majority of cases but may be delayed to the third decade.[36] Cysts of the septum pellucidum have been recognized as the cause of increased intracranial pressure, mental retardation, and convulsions.[174]

A large group of neurologic disorders has been classified as "heredofamilial or degenerative." Most of the diseases in this group are not congenital, yet there can be little doubt that they are prenatally determined. Most of them are inherited as dominant, recessive, or sex-linked recessive diseases, but it should be remembered that similar clinical entities may be transmitted in different families as different genetic entities. Thus, spastic paralysis is sometimes inherited as a dominant and sometimes as a recessive trait. Friedreich's ataxia may be dominant, recessive, or sex-linked recessive. Such differing behavior must be taken into account when a eugenic prognosis is attempted. Most of the patients are born apparently normal and develop manifestations of their disease at some time after birth. As a rule, the diseases of this group progress steadily and incapacitate the patients increasingly. The term "abiotrophy" has been used for this behavior because an inherited lack of vitality of the central nervous system seemed to be characteristic of these diseases.

In recent years this "lack of vitality" has been better defined in certain cases as an inherited disturbance of metabolism or of enzyme action which slowly destroys parts of the nervous system in postnatal life. The storage diseases belonging in this group have been mentioned above. A disturbance in copper and amino acid utilization has been found in patients with hepatolenticular degeneration (p. 89). The nervous symptoms of acute porphyria are due to an inherited disturbance or porphyrin metabolism (p. 90). It is hoped that similar chemical anomalies will be found to be the inherited basis of the degenerative disorders of the nervous system. It is not necessary to describe and discuss these disorders here in detail. But it is pertinent to this review that some of them take a very protracted course and incapacitate the patients for many years. Friedreich's ataxia, peroneal muscular atrophy, cerebral sclerosis of Pelizaeus-Merzbacher, Huntington's chorea, spastic paraplegia, hereditary myoclonus epilepsy, and others exemplify this group.[75]

It has been mentioned that many *tumors* of the central nervous system occurring in children are either malformations or derived from them. Globus, Zucker, and Rubinstein[86] concluded from a clinical and anatomic survey of tumors prevalent in children and adolescents that "the autochthonous blastomatous tumors predominate, an observation which supports the view that cerebral neoplasms in the majority of instances probably originate from embryonal rests. The best examples of such tumors are craniopharingioma, pinealoma, ependymoma and hemangioendothelioma."

Congenital word deafness, congenital word blindness, and congenital aphasia attributable to developmental disturbances of the brain represent serious educational and social problems.[75]

Cerebral palsy is one of the most important causes of crippling, accounting for more than 10 per cent of the number of crippled children on State Registers.[198] It is important, therefore, to ascertain the injurious factors responsible for this group of disorders. There is general agreement that cerebral palsy is neither a clinical nor an etiologic entity and that prenatal, paranatal, and postnatal factors may result in disease pictures covered by the general term "cerebral palsy." Unfortunately, there is wide disagreement concerning the relative importance of these factors in the etiology of this form of crippling. This disagreement is explained in part by the difference of the patients seen by various specialists. Orthopedic surgeons examine a different group of patients with cerebral palsy from physicians in mental institutions. In addition, there is often an intermingling of adverse factors which resists etiological analysis. A child damaged in prenatal life may undergo abnormal delivery and suffer damage from postnatal infection or trauma. It is easily understood that such a case could be attributed to prenatal, paranatal, or postnatal factors. Pohl[158] considers only 18 per cent of a series of patients with cerebral palsy attributable to prenatal factors, but Stewart[184] thinks that the majority are of prenatal origin and concludes that birth injury has in the past been overestimated. Yannet[224] supports this conception in a study of mentally deficient children with cerebral palsy. The prenatal origin of the disorder can be demonstrated by suggestive family histories and by the presence of obvious congenital malformations in the patients indicating injury in fetal life. It is not possible to give a quantitative estimate of the role played by developmental defects, but neuropathologic studies indicate that many disorders of prenatal origin result in the symptoms of cerebral palsy. Microcephaly,[184] arrested hydrocephaly,[66] microgyria, pachygyria,[75] cerebellar atrophy,[184] agenesis of the corpus callosum,[89] diffuse and tuberous sclerosis, congenital demyelinating encephalopathy,[219] congenital encephalomalacia with cavity formations, agenesis of white matter,[203] and many other pathologic changes of the brain of prenatal origin may explain some of the clinical syndromes often attributed to birth injury. It is clear that this segment of cerebral palsy cannot be eliminated by improved obstetrical care but must be considered together with the problem of congenital anomalies.

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MUSCULAR DEFECTS

Congenital absence of muscles is occasionally encountered. The defect may be unilateral or symmetrical; sometimes muscle defects are associated with

congenital defects of other organs. Absence or defect of the pectoral muscles has been most often observed, followed in frequency by defects of the trapezius, serratus anticus, and quadratus femoris. Congenital *defect of the pectoral muscle* may be accompanied by absence of the mammary gland, syndactylism, and microdactyly.[1] Congenital *defects of the abdominal musculature* are often associated with anomalies of the ureters, bladder, and sex organs. Infections of the respiratory and urinary tracts and difficulties of defecation complicate this disease picture and shorten the life span of affected children.[178]

Congenital facial diplegia has been described as a syndrome consisting of bilateral paralysis of facial and ocular muscles. The eyes cannot be closed completely, nursing is difficult, and facial expression does not develop. Facial diplegia is often accompanied by strabismus, pectoralis defects, club foot, deafness, or mental deficiency.[99]

Congenital contractures of muscles are of great practical importance since they contribute to the causes of crippling. *Clubfoot* accounts for 7.4 per cent of children on State Registers because of crippling.[198] In some studies abnormal muscle fibers have been demonstrated in early embryonic life, but it is not clear whether such changes are due to retarded development or to faulty innervation. Genetic factors play a role in some cases of clubfoot and fetal malposition in others. Clubfoot occurs in many children with multiple congenital malformations and no simple etiological factor can account for the different forms. *Congenital torticollis* is due to unilateral shortening of the sternocleidomastoid muscle and accompanied in many cases by asymmetry of the face and skull. In some patients anomalies of the cervical vertebrae indicate an early developmental error, but other cases may be caused by birth trauma or abnormal intrauterine position. *Arthrogryposis multiplex* or amyoplasia congenita is a seriously crippling disorder of the muscles and joints. Usually the arms are extended at the elbows and the legs flexed at the hips and knees. The hands and feet assume various abnormal positions. The rigidity may be so pronounced that delivery is difficult. Dislocations of the joints, a variety of skeletal malformations, or hydrocephalus may be combined with the muscular anomalies. Most cases are sporadic, but heredity has been observed in some instances.[183]

Progressive muscular dystrophy (Duchenne) is usually recognized within the first few years of life, but not at birth. It is probable, however, that the basic anomaly is congenital, although the first signs of weakness are not recognized before the child begins to walk. Heredity can be demonstrated in many pedigrees, sex-linked recessive or simple recessive inheritance being the rule. The disease picture is easily recognized by the typical gait, the posture, and the way of getting up from a supine position. The plight of the patients and of their families is well-known. The children are usually chairridden in their first decade, and bedridden in the second, when death terminates their life. The milder, fascioscapulohumeral form of muscular dystrophy (Landouzy-Déjerine) may begin later than the one just mentioned, and heredity is not always demonstrable. Muscular weakness usually begins in the arms and in the shoulder girdle. The degree of disability varies, but arrest of the disease may occur and survival be prolonged. Although this muscular dystrophy has often a late onset, its con-

genital nature is suggested by congenital absence of muscles in persons who later become affected. Absence of the pectoral, brachioradial, or femoral muscels may be noticed at birth.[1] *Myotonic dystrophy* is often combined with cataract and testicular atrophy. Although the onset of muscular manifestations is usually late, cataract may be discovered by the use of a slit lamp at an earlier age. Mental deficiency is present in some of the cases in early childhood. *Myotonia congenita* (Thomsen's disease) is an inability to relax contracted muscles at will. The condition is dominantly inherited in some pedigrees, but sporadic cases occur also. Affected persons are unable to perform certain coordinated motions and must forego some physical activities. However, they can live useful lives as shown by the fact that several patients of this type were physicians who reported their own cases.[1]

MALFORMATIONS OF THE EYE

The role of prenatal pathologic factors inducing ocular defects is well appreciated. As the incidence of ophthalmia neonatorum and syphilis decreased, visual disturbances of prenatal origin assumed increasing importance. Sorsby[181] states that today children blinded by ophthalmia neonatorum or other infectious diseases are seen only exceptionally, and that in the greatly reduced numbers at blind schools congenital malformations and genetic disease now predominate. The causes of blindness among pupils in schools for the blind were considered to be prenatal in 58.1 per cent.[117] Some of the disorders resulting in blindness or serious visual disturbances are frank congenital malformations: megalophthalmos, microphthalmos, anophthalmos, orbital encephaloceles, embryotoxon, sclerocornea, persistent pupillary membrane, dislocation of the lens, congenital cataract, coloboma of the iris and choroid, macular cysts, and congenital atrophy of the optic disc belong in this category. Other anomalies of the eye are associated with general disorders of prenatal origin such as amaurotic familial idiocy, gargoylism, cystinosis, galactosemia, or albinism. These diseases are now attributed to inborn errors of metabolism. Prenatal rubella and toxoplasmosis may cause severe ocular anomalies and blindness. Skeletal disorders involving ocular complications are the craniostenoses, marble bone disease, Marfan's syndrome, Marchesani's syndrome, and chondrodystrophia calcificans congenita. Congenital obstruction of the nasolacrimal duct and anomalies of ocular movement are less dangerous to vision but cause protracted difficulties to the patient. Among the tumors of the eye, dermoids, hemangiomas, retinoblastomas, and primary tumors of the optic nerve in Recklinghausen's disease are of prenatal origin. "Abiotrophies" of the eye are not congenital disturbances but are determined by prenatal factors. The retinitis pigmentosa group, macular dystrophies, choroideremia, and choroidal sclerosis may be mentioned as examples.[77]

MALFORMATIONS OF THE EAR

The separation of prenatal and postnatal factors responsible for deafness is admittedly difficult. Data contained in statistics are not always based on a thorough medical examination. The effects of birth traumas or early infectious after birth may be mistaken for congenital deafness. On the other hand, trauma

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or infection may be superimposed on developmental defects of the ear and be considered "the cause" of the hearing defect. Parents dislike to admit that a child was born deaf and prefer to relate deafness to trauma or disease. Modern treatment of ear infections is responsible for a marked change in the percentage distribution of causative factors. Finally, it should be pointed out that the interior of the ear is not open to inspection like that of the eye, which makes it difficult to recognize developmental errors of the middle and inner ear before they are masked by postnatal secondary changes.

According to Best,[20] 41.5 per cent of the deaf in the United States are classified as congenital cases, and deafness in school children is considered to be congenital in 62 per cent. In 1927 a survey of 3,120 children in institutions and schools for the deaf was made in the Chicago area and in 61.8 per cent the deafness was classified as congenital. In a smaller but thoroughly studied group of preschool and school children the cause of deafness could not be determined in 104 of 296 patients.[28] Of the 192 children with a known etiological factor, 99 (45.9 per cent) had been exposed to the causative factor by the time their delivery had been completed. Since this percentage includes prenatal and paranatal factors, the estimate of congenital deafness is relatively low in this group. But the authors emphasize that, in compiling such a list, one frequently has the difficult choice between several possible etiological factors.

Sporadic deaf-mutism is due to various developmental anomalies of the labyrinth and auditory nerve. About 70 per cent of these cases are attributed to malformations of the sacculus and cochlea.[130] Heredity plays an important role in congenital deafness. It is very likely that hereditary deaf-mutism is not a genetic entity, a circumstance which explains the lack of agreement concerning its mode of inheritance.[83] Labyrinthine deafness and otosclerosis are not congenital, as a rule, but a prenatal origin is suggested by their heredity. A variety of congenital malformations of the middle ear[6] may result in loss of hearing.

The association of *deafness with generalized syndromes* of abnormal development suggests that such cases are prenatally determined although loss of hearing may not become apparent until later in life. Osteopsathyrosis or osteogenesis imperfecta consists in the triad of brittle bones, blue scleras, and otosclerosis. Changes of the osseous labyrinth occur in chondrodystrophy.[149] Loss of hearing is the rule in mandibulofacial dysostosis,[76] a syndrome of malformations of organs derived from the first visceral arch and involving various parts of the ear. In osteopetrosis, deafness may develop by osseous overgrowth and constriction of the auditory nerve through the internal auditory meatus. Skeletal malformations such as craniostenosis or the Klippel-Feil syndrome are complicated by loss of hearing. A variety of aural malformations have been described in oxycephaly.[7] In craniofacial dysostosis[45] anomalies of the external auditory meatus, of the ossicles, and of the mastoids result in reduced hearing.[148] Loss of hearing is the rule in gargoylism. In this condition as well as in the craniostenoses and in mandibulofacial dysostosis, there is a marked tendency to infections of the middle ear. Susceptibility to aural infections is sometimes found in families which appear normal otherwise. The anatomic basis for such a tendency has been found in congenital anomalies of the mucous membranes and of the mastoid

process.[2] Atresia of the external auditory meatus is usually combined with malformations of the middle ear.[7] Congenital deafness is sometimes associated with retinitis pigmentosa in a hereditary syndrome.[181] A metabolic disturbance may be the basis of this combination of defects.[110]

Congenital deafness is not always hereditary, but may be due to prenatal environmental injuries. *Endemic deaf-mutism*, though not a problem in the United States, was an important cause of deafness in other countries. Owing to iodine deficiency-goiter and hypothyroidism of the mother, the inner ear and the middle ear of the fetus undergo changes in this condition which cannot be corrected by thyroid therapy after birth.[55] But prenatal iodine prophylaxis reduces the incidence of endemic deafness together with that of cretinism. Maternal rubella during the first four months of pregnancy may cause deafness with or without associated congenital malformations in the child.[91,188] Pathologic changes of the sacculocochlear type of deaf-mutism have been demonstrated in some of these cases.[129] The percentage of deafness attributable to prenatal rubella varies greatly in different countries according to the incidence of rubella in adults.[129] In the Audiology Unit of a London hospital congenital perceptive deafness was found in 891 of 1,806 deaf children. Sixty-nine cases were classified as "maternal rubella deafness" and 50 as hereditary. In the same group were 27 children who were thought to be deaf because of hemolytic disease in the newborn period associated with isoimmunization.[73] Taylor[193] reported several cases of congenital deafness due to quinine medication during pregnancy.

Some of the tumors resulting in loss of hearing have a prenatal origin. The dermoids and the true cholesteatomas of the middle ear are considered as heterotopic new formations derived from congenitally displaced epidermal elements.[6,7] Bilateral acoustic neuroma may be transmitted as a dominant hereditary trait. Although symptoms do not become manifest in early life, the basic anomaly, thought to be neurofibromatosis, must be considered a congenital anomaly.[81]

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SKELETAL MALFORMATIONS

Among the crippling disorders, some syndromes must be mentioned in which skeletal malformations dominate the disease picture although other organs are also involved. Such syndromes contribute greatly to chronic disability because of the multiplicity of symptoms. Heredity plays an important role in the etiology of these disease pictures. *Chondrodystrophy* is a well-known congenital osseous anomaly resulting in a typical form of dwarfism. The skeletal anomaly may be combined with malformations of other organs, but achondroplastic dwarfs surviving infancy are often free of associated anomalies. In the introduction *arachnodactyly* (Marfan's syndrome) was mentioned and was chosen as an example of a syndrome which affects so many organ systems that no single specialty can provide treatment of the patients or assume responsibility for etiologic investigation. There are other syndromes which disable their bearers because of multiple anomalies. *Osteogenesis imperfecta tarda* or *osteopsathyrosis* is a condition characterized by brittle bones which break on slight provocation. Repeated fractures during childhood cause a great deal of disability and require orthopedic care and hospitalization. In severe cases the patients develop de-

formities of the spine and of the extremities. Flaccid ligaments and hyperextensible joints are additional symptoms. Consequently, these children have an increased tendency to sprains and dislocations. About one-fourth of the patients develop deafness in later life. *Fibrous dysplasia* represents a very different skeletal disorder which also leads to fractures, pain, dysfunction and bowing of the affected bones. Affected limbs are often deformed, particularly when subjected to weight-bearing; coxa vara and genu valgum are frequently present. The osseous changes are not noticed at birth but the prenatal origin of the disorder is suggested by congenital abnormal pigmentations of the skin which sometimes accompany the skeletal manifestations. Endocrine disturbances may be associated with this disorder (p. 80).

Cleidocranial dysostosis is due to retarded ossification of membranous as well as cartilaginous precursors of bone. The name of the syndrome is derived from its most striking features: congenital absence of the clavicles combined with softness of the calvarium. It is now recognized, however, that ossification of cartilage and dentition are also delayed. The main symptoms interfere little with the patient's health, but in many cases deformities of the spine, coxa vara, and genu valgum develop. Pressure of a clavicular fragment on the brachial plexus may cause serious symptoms. The teeth show marked irregularities and a great tendency to decay. The patients are usually of small stature.

The *Klippel-Feil syndrome* is an anomaly of the spine characterized by congenital fusion of two or more cervical vertebrae. This vertebral anomaly is a representative of many related developmental conditions and it is very likely that its etiology is not unitary. The patients are characterized by a short neck, low hairline in the back, and webbing of the neck. Some bearers of this anomaly are free of symptoms, but most of them have many complaints. The mobility of the neck is reduced, the vertebrae adjacent to the fused bones have an increased tendency to fractures. Difficulty in breathing and swallowing has been described in children. Association with mediastinal cysts has been observed repeatedly (p. 68). Scoliosis or kyphoscoliosis of the lower spine develop in many cases. A variety of neurologic complications have been described. Mirror movements interfering with certain motor functions are often observed. Owing to narrowing of the foramina, nerve roots may be compressed and hyperesthesia and paralyses develop. Late complications such as spastic paralysis, syringobulbia, syringomyelia, and ataxias have been reported. Platybasia, oxycephaly, cleft palate, micrognathia, and other deformities may be present. Cardiac anomalies, deaf-mutism, or mental deficiency occur in some of the patients.[177]

In *Morquio's disease*, an atypical chondrodystrophy, the vertebral bodies are low and irregularly formed, the intervertebral spaces are reduced in height and abnormal curvatures of the spine are the rule. A relationship to the Klippel-Feil syndrome is suggested by the occurrence of platybasia and by abnormal segmentation of cervical vertebrae in some of the cases. The patients usually appear normal at birth; but within the first years of life they develop kyphosis, pigeonbreast and knock-knees, symptoms which can be mistaken for rickets. Later the joints show swelling and limitation of movements. Changes in the hip joint account for the crouching position of the patients who appear markedly

dwarfed. Muscular development is poor and the ligaments are flaccid. If the cervical cord is compressed by the abnormal vertebrae, paralysis of the extremities, reflex changes and muscular atrophy may develop. Although most of the symptoms appear in postnatal life, there can be no doubt that the disorder is determined before birth. Several members of a family may be affected and recessive or sex-linked recessive inheritance[83] has been demonstrated in many pedigrees.

Gargoylism is similarly inherited and clinical manifestations appear in postnatal life. The underlying pathologic process differs from Morquio's disease in that an abnormal intracellular substance is deposited in large "gargoyle cells" which can be found in many tissues.[187] The involvement of soft tissues in the disease process causes a variety of symptoms. In addition to the "gargoyle" facies and the malformations of the skeleton, hepatosplenomegaly and cloudiness of the corneas make their appearance. The brain substance is reduced and internal hydrocephaly and mental deficiency develop. The nose and the ears are subjected to frequent infections, and deafness is the rule. The disease process involves often the valves and the endocardium of the heart, and cardiac hypertrophy is present in most of the cases. Dyspnea is noticed on slight exertion, and cyanosis is seen in advanced cases. The abdomen is distended, and hernias are present. Dwarfism becomes more pronounced as the patients become older. The joints are forced into abnormal positions, and the movements of the extremities are limited. Neurological symptoms such as convulsions, ankle clonus, hyperactive tendon reflexes, spastic paraplegias, and ataxias are observed. Such patients may live for many years and present many medical and social problems.

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Osteopetrosis or marble bone disease is sometimes discovered accidentally in roentgenograms, but in severe cases symptoms become manifest at an early age. The abnormal structure of the bones predisposes to fractures, rickets, and to osteomyelitis. Narrowing of the foramina in the base of the skull may result in loss of vision and hearing. Anemia is an associated symptom of osteopetrosis, and subdural hematomas occur rather frequently.

Multiple exostoses are usually inherited as a dominant trait. They may remain symptomless or cause a variety of pathologic manifestations. They may lead to deformities, small stature, impairment of mobility, or to the development of chondrosarcoma. Pressure of the osseous excrescences on nerves result in pain, paraesthesias, paralysis, and even deafness. Compression of the spinal cord may also produce neurological symptoms. These examples suffice to illustrate the multiplicity of symptoms which may be elicited by syndromes usually considered as skeletal anomalies.

CARDIOVASCULAR MALFORMATIONS

The congenital nature of malformations of the heart and great vessels is so well recognized that little need be said here about this subject. Cyanosis or murmurs betray the presence of many cardiac defects at an early age, thus directing attention to these malformations. Physicians have been interested in congenital cardiac anomalies since the eighteenth century.

In spite of this early and intense interest, it is still difficult to obtain statistical data on the incidence and outcome of congenital cardiac defects. Murmurs heard in the neonatal period are not always due to permanent structural defects and may disappear in later life. It is known, on the other hand, that signs and symptoms of congenital cardiac malformations may not become manifest before adult life. The ratio of congenital to acquired heart disease decreases constantly with increasing age; it is also dependent upon geographical factors. Statistical data are further influenced by the methods used to obtain them. This was clearly brought out in a recent planned study of over 6,000 infants born and examined at the Columbia-Presbyterian Medical Center in New York City[166] where a special effort was made to discover congenital malformations with modern diagnostic methods. The over-all incidence of cardiovascular malformation was 0.83 per cent, which is more than ten times the incidence ascertained by previous investigators.[54,137] The high estimate includes stillborn infants and those who die within the first month.

In an English study in which estimates were based on records from various sources, 0.37 congenital cardiac defects per hundred live births were found.[135] There is general agreement that the mortality of infants with cardiac malformations is very high, but two-thirds of the affected children may survive for more than two years[166] and about one-third reach the tenth birthday.[135] As congenital heart disease decreases in frequency with advancing age, the acquired forms of heart disease play an increasing role. In a cardiac clinic in New York, all the children under 3 years had congenital heart disease, but the incidence was only 11 per cent in children over 12 years.[204] In children of school age affected with heart disease, about one-half have congenital defects;[162] the relative role played by acquired cardiac disease is apparently higher in the East[204] than in the West.[171] Among children of school age ventricular septal defects and open ductus are the diagnoses most frequently entertained.

Congenital malformations of the heart are often combined with defects in other organ systems. In young age groups[166] and in autopsy material,[87] associated malformations are found in over one-third of the children with congenital cardiac defects. A well-known syndrome in which congenital heart anomalies are frequently present is mongolism. It is estimated that about two-thirds of the children born with mongolism and one-third of those surviving the second year have cardiac defects.[166] Ventricular septal defect is the most common anomaly, but in mongols who die young ostium atrioventriculare commune is often found. Another syndrome of mental deficiency and congenital heart disease is caused by prenatal rubella.[91] Cataract, cleft palate, diaphragmatic hernia, intestinal malrotation, situs inversus, esophageal atresia, and many other malformations may be associated with congenital heart disease.

In this discussion the cardiac malformations compatible with life are of prime interest since they are likely to result in chronic illness. *Defects in the ventricular septum* may cause little disturbance throughout life. However, high and large ventricular defects sometimes cause changes in the pulmonary artery, dilatation of the pulmonary bed, and cyanosis.[192] Acute and subacute bacterial endocarditis may complicate the defect. Patency of the *ductus arteriosus* is

another anomaly found frequently in children surviving infancy and in adults. Persons with this defect often enjoy good health for many years, but without surgical correction the life expectancy is markedly reduced.[118] Subacute bacterial endocarditis, congestive heart failure, and other complications endanger patients with persistent ductus arteriosus. This anomaly is the most frequent cardiac defect in children with the prenatal rubella syndrome. Defect of the *auricular septum* is of interest because it represents a congenital anomaly which often fails to become manifest during childhood. It is estimated that in about one-half of the cases the defect remains undetected before the age of 18 years. However, auricular defects may ultimately lead to serious disability and death.[38] Superimposed rheumatic infections, subacute bacterial endocarditis, cardiac arrhythmias, frequent pneumonias, and pulmonary emboli are complications. It is said that patients with this septal defect have a definite constitutional habitus, characterized by long and gracile bones, frail body build, and delayed puberty.[192] The association with arachnodactyly is of theoretical interest, since this syndrome is often dominantly inherited. Thus some auricular septal defects are genetically influenced. Patients with "spider fingers" develop also aortic changes, such as aneurysms, stenosis, and coarctation. Some of these changes are attributed to cystic necrosis of the media, but the basic defect is probably in the elastic and muscle fibers, which are abnormal throughout the body. The association of a gross congenital cardiac malformation with tissue anomalies leading to postnatal cardiovascular diseases illustrates the multiple effects of a "pleiotropic" gene. Congenital heart disease may also be a constituent of recessively inherited syndromes such as chondrodystrophia calcificans, the Laurence-Moon-Biedl and Ellis-van Creveld syndromes, situs viscerum inversus, and others. In gargoylism congenital heart disease is often diagnosed but it is likely that the murmurs heard in these patients are due to thickening of the valves and shortening of the chordae. These valvular changes develop probably in postnatal life but they are caused by accumulation of vacuolated connective tissue cells which are a manifestation of the inherited storage disease.[187]

Most of the cardiac malformations of the cyanotic group are incompatible with life, and the life span of children afflicted with them is usually short. The *tetralogy of Fallot* and other forms of pulmonary stenosis carry a better prognosis, and patients with these anomalies may live for many years. The prognosis varies with the degree of pulmonary stenosis and with the nature of associated cardiac defects. Patients with the cyanotic forms of congenital heart disease suffer from dyspnea on exertion and their physical activities are often limited. In cases of marked polycythemia, thromboses may occur and lead to cerebral accidents. Acute or subacute bacterial endocarditis represents another complication leading to protracted illness. These patients are chronically ill, but many cases can now be helped substantially by surgical measures which establish an increased blood flow to the lungs.

The primitive aortic arch system undergoes peculiar changes during embryogenesis in higher species. While some of the aortic arches show marked growth and development, others become obliterated at the same time. This intricate

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process of differentiation is easily disturbed by various interfering processes, and as a result *malformations of the aortic arch* system ensue. Such malformations are often compatible with life and good health and are discovered as accidental findings in roentgenograms or at autopsy. In other cases they interfere with the normal circulation so seriously that viability is endangered. In infants they may cause acute disturbances of respiration and nutrition. There are also instances of delayed and chronic manifestations which affect older children or adults. *Dysphagia lusoria* is due to an abnormal course of the right subclavian artery which arises from the left side of the aortic arch and passes to the right behind the esophagus. By compression of the esophagus difficulties in swallowing are liable to occur. Patients may notice this dysphagia, caused by a congenital anomaly, late in life, since arteriosclerosis or hypertension may aggravate the situation. Palmer[155] stressed the seriousness of this condition in older patients who are plagued not only by dysphagia but also by fear and mental depression. As long as the source of their disturbance remains unexplained, they worry about having cancer or other serious diseases. Without knowledge of this anomaly and proper x-ray examination physicians may consider the complaints as psychogenic and the patients as hypochondriacs. *Rings* formed by aortic arches and encircling the trachea and esophagus are likely to result in dysphagia and dyspnea.

Coarctation of the aorta of the "adult type" is compatible with health in many instances, but serious complications occur in the majority of cases. Sometimes the anomaly becomes the seat of infection or sclerosis. Aortic aneurysm or rupture proximal to the obstruction may occur. Hypertension in the upper part of the body is common. The patients complain of severe headaches and burning sensations in the hands and face. Cerebral accidents or cardiac failure occur as fatal complications.[192] Coarctation of the aorta has been repeatedly observed in patients with ovarian agenesis (Turner's syndrome).

The few examples cited show that congenital cardiovascular malformations are sometimes at the root of chronic disease and disability which in some cases do not appear before adolescence or adult life. Without specific diagnostic examinations or autopsy the basic malformations may remain unrecognized. Treatment is often aimed at the complications and not at the underlying anomaly. This situation has improved in recent years since surgical correction of some anomalies has become possible and the importance of the recognition of the malformations has been stressed.

The earliest blood vessels of the embryo consist of simple endothelial tubes which form plexuses by multiple communications. These primitive blood vessels change their course and width many times during embryonic development, and formation of new blood vessels as well as retrogression of established channels is a normal occurrence. When differentiation into arteries and veins begins, there exist many communications between the two types of vessels, but normally atrophy of most of the channels takes place with the exception of the capillaries, which remain the only connections between arteries and veins. Under pathologic conditions noncapillary communications persist in the form of *arteriovenous aneurysms*, which represent, therefore, malformations due to arrested

development. In contrast to acquired arteriovenous aneurysms, congenital communications are usually multiple.[103,106] They may be diagnosed at birth or go unnoticed for many years when abnormal growth or pulsations direct attention to the anomaly. If an extremity is involved, hypertrophy and bruits and thrills over the fistula render the diagnosis possible. In some cases hypertrophic arthritis and ulcers develop in the affected extremity. Symptoms appear often after a traumatic incident, and the congenital nature of the anomaly is overlooked. The fistulous tracts may cause systemic defects and bring about cardiac hypertrophy.[106]

Arteriovenous fistulas of the neck result in signs and symptoms which may lead to an erroneous diagnosis of rheumatic heart disease. A cardiac murmur may be heard, but radiation of the murmur to neck and skull will direct attention to the possibility of a cervical anomaly.[190]

Intracranial arteriovenous malformations consist of a tangle of abnormal, undifferentiated blood vessels of varying caliber and size. Symptoms are often discernible during childhood, but some of the cases are not recognized before adult life. Headaches, attacks of unconsciousness, nausea, vomiting, epileptiform seizures, and mental deterioration may occur. Cerebral angiography makes possible visualization of the location and size of the anomaly. Surgical extirpation or radiation therapy can give relief, but the ultimate prognosis is grave and the patients endure years of epileptic seizures, severe headaches, recurrent subarachnoid hemorrhages, and often hemiplegia.[175]

Pulmonary arteriovenous fistulas establish direct communication between pulmonary arteries and veins thus permitting the entry of some nonoxygenated blood into the systemic circulation. If the shunt is significant, dyspnea, cyanosis, clubbing, murmurs, and polycythemia result. Such cases simulate congenital heart disease, but roentgenographic demonstration of the anomaly leads to the correct diagnosis. This congenital anomaly is often a disease of adult life, since it usually takes many years before disturbing manifestations develop. Many cases occur in patients with hereditary hemorrhagic telangiectases (p. 75), and repeated epistaxis is usually one of the earliest symptoms. Surgical removal of the fistula was considered the cure for this condition, but the prognosis must be guarded since multiple vascular lesions are often present in both lungs.[11]

Hemangiomata of the liver may lead to signs and symptoms of congenital heart disease and result in early cardiac failure.[220]

Lindau's disease is a hamartosis which involves many organs. It is discussed here because the outstanding symptoms are caused by vascular anomalies which date back to prenatal developmental errors. In spite of the congenital nature of the basic changes, symptoms do not develop, as a rule, before the third or fourth decade of life. Angiomas of the retina, of the cerebellum, or of the spinal cord may be found. Loss of vision or symptoms of cerebellar tumor are the most conspicuous manifestations. The brain tumors which arise in the hemispheres of the cerebellum consist of relatively small angioreticulomas. These produce a transudate by circulatory stasis and later cysts which are much larger than the original tumor. It is their growth that brings about symptoms of increased intracranial pressure. In the spinal cord angiomas, gliomas and syrin-

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gomyelia may develop. Cysts of the pancreas are sometimes present. They may be symptomless, but diabetes has been observed in Lindau's disease. Cysts of the kidney and hypernephroma are sometimes found in affected persons. This hamartosis occurs sporadically, but striking pedigrees showing dominant inheritance have been reported.[128] In such families cerebellar tumor with or without angioma retinae, spinal disorders,[120] or diabetes[25] may appear in the pedigree. This wide array of manifestations can be attributed to an abnormal dominant gene with pleiotropic effects.

Intracranial aneurysms are of great clinical interest and several monographs have been devoted to this subject.[48,96,167] Although some authors assumed that such aneurysms are congenital,[48] this point of view is not generally accepted. It is very likely that the aneurysmal sac is not present at birth, but a defect in the arterial wall may be congenital. The association of berry aneurysm with other congenital malformations speaks for their teratologic nature. Intracranial aneurysm has been found combined repeatedly with polycystic renal disease[23] or with coarctation of the aorta.[223] A familial incidence of congenital aneurysms of cerebral arteries has also been observed.[37]

MALFORMATIONS OF THE RESPIRATORY TRACT

Congenital malformations of the respiratory tract go often unrecognized, particularly if their complications dominate the disease picture: bronchitis, asthma, chronic pneumonia, or congenital heart disease are frequently diagnosed, while the basic disorder is overlooked. However, modern techniques of clinical examination now permit the correct diagnosis intra vitam in many cases, and surgical procedures can relieve acute and prevent chronic illness.

Bilateral *congenital atresia of the posterior nares* may lead to suffocation in the neonatal period or result in feeding difficulties. Unilateral atresia causes chronic obstruction and purulent discharge which can be relieved by surgical measures.[16] *Encephaloceles* protruding into the nasal cavity may cause obstruction. They must be distinguished from polyps and other nasal tumors. Prolonged respiratory difficulties occur in infants with *micrognathia* and posterior cleft palate (Pierre-Robin syndrome). The tongue may occlude the air passage in such cases and feeding becomes a difficult problem.

Congenital malformations of the larynx are not extremely rare. Infants with such anomalies are sometimes mistaken for cardiac patients because of cyanosis. Malformations of the epiglottis, webs, congenital cysts, and others can be discovered by direct laryngoscopy. Hemangioma of the larynx causes recurrent respiratory difficulties, bronchitis, and pneumonia. Direct laryngoscopy does not always reveal this congenital growth, which may be located under the glottis.[50] A concomitant external hemangioma may assist in the correct diagnosis. Congenital malformations of the trachea, bronchi, and lungs were reviewed by Holinger and his associates.[102] Congenital stenoses due to deformities of tracheal cartilages may result in chronic respiratory obstruction with inspiratory and expiratory stridor. Tracheoesophageal fistulas are often associated with strictures of the trachea. These may cause continued respiratory difficulties before and after surgical anastomosis of the esophageal segments. ***Congenital malacia of the larynx, trachea, or bronchi*** results in stridor, dyspnea,

and attacks of cyanosis. Congenital vascular rings are sometimes accompanied by anomalies of the tracheal cartilages located at the site of the vascular anomaly. In such cases relief of the vascular constriction by operation may fail to abolish the dyspnea, dysphagia, and cyanosis of the patients. Tracheoceles or tracheal cysts can lead to progressive respiratory obstruction, constant wheeze, and cough. Bronchial webs causing partial obstruction of the lumen produce obstructive emphysema or atelectasis.

Absence of one lung is sometimes well tolerated. Dyspnea occurs on exertion and an increased susceptibility to infections exists.

Congenital pulmonary cysts represent a complex problem pathologically as well as clinically. They are divided, as a rule, into cysts of bronchogenic and cysts of alveolar cell type. Small and scattered cysts which communicate with the bronchi are sometimes classified as congenital or mistaken for acquired bronchiectases. In contrast to acquired bronchiectases, such cysts are found often in the upper lobes of the lungs. As frequent infections complicate these malformations, their teratologic origin becomes obscured.[42] Wolman[221] stresses the lack of correlation between the pathologic and clinical appearances of lung cysts. Air-containing and fluid-containing cysts can be distinguished clinically. The latter type may be symptomless, but by secondary infections a picture of chronic empyema may be simulated. Such fluid-containing cysts can be mistaken also for chronic pneumonia, tuberculosis, lung abscess, or mediastinal tumor. Children having air-containing cysts may have few symptoms with the exception of cough and expectoration. However, superimposed infections can alter the picture and differentiation from acquired bronchiectases becomes difficult.[221] Pneumonia, tuberculosis, or pneumothorax may also be imitated by complications of air-containing cysts. To diagnose congenital cysts in adults is even more difficult. Such cysts sometimes remain symptomless to the third or fourth decade, when repeated respiratory infections, cough, fever, or hemoptysis make their appearance.[42] Cystic pulmonary malformations are probably not so rare as is usually assumed, but they often go unrecognized or are listed under different names. Cooke[42] found 24 synonyms under which cases of cystic disease of the lungs are reported. Such malformations are usually benign in persons reaching adulthood. One of their dangers lies in the possibility that they may be mistaken for more serious conditions when discovered by accident. If an erroneous diagnosis of tuberculosis, empyema, or pneumothorax is made, the patient may be exposed to unnecessary and damaging treatments.

An important functional anomaly of the lining of the respiratory tract is associated with *cystic fibrosis of the pancreas* (p. 70). Before this entity was recognized, cases of this type were often diagnosed as chronic pneumonia, bronchiectases, asthma, or whooping cough. It is now assumed that a congenital anomaly of the mucous glands of the trachea and bronchi is responsible for the great variety of respiratory symptoms of this disease.

MALFORMATIONS OF THE ALIMENTARY TRACT

Malformations of the alimentary tract are not rare. Some of them, which are recognizable by external inspection, are well-known and reparable to a certain

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extent by plastic surgery. *Harelip and cleft palate* occur in about one per thousand of the population. The severest forms are often accompanied by malformations incompatible with postnatal life while those not complicated by other anomalies of the body are an important cause of disability. They require special nursing care and the help of pediatricians, surgeons, orthodontists, and speech therapists. The expenses of adequate palliative measures are a serious financial drain to the average family, and cleft palate accounts for 4 per cent of the crippled children on State Registers.[198]

Imperforate anus, though rarer than cleft palate, presents another teratologic problem of the intestinal tract. Some forms can be successfully relieved by incision of the anal membrane followed by dilations of the constricting ring. If, however, the rectal pouch ends blindly some distance above the anus or fistulas complicate the situation, surgical relief is more difficult. In some cases sigmoidostomy is established and maintained for one or two years. In other children an abdominoperineal approach can be attempted soon after birth,[93,165] and good results are obtained by surgeons especially trained in this field. However, many of these children whose lives have been saved by operation are disabled by anal scarring or neuromuscular injuries to the perineal area. Anal tightness, perineal laxity, and persisting fistulas may cause chronic difficulties.

Many internal malformations of the intestinal tract cause vomiting, dehydration, loss of weight, distention, dyspnea, and often death in the neonatal period. Most cases of this type, which now can be recognized as malformations in the living infant, were in the past attributed to gastroenteritis, birth injury, pneumonia, and other postnatal or perinatal factors, unless autopsy revealed the true nature of the disease.

The *esophageal atresias* can be treated successfully by surgery, and children with such anomalies may now survive. However, even expert surgical treatment cannot convert all children with these malformations into healthy persons. Esophageal atresias are often associated with congenital malformations of the heart, the intestine, the anus, or the urogenital tract. Infants with such complicating anomalies may require several operations and many months of hospitalization.[93] A tendency to recurring respiratory infections and difficulty in swallowing bring some of these patients back to the hospital many times. Tracheal fistulas and secondary esophageal strictures represent often vexing problems which delay recovery of the child. Congenital *stenoses* or *strictures* of the esophagus causing only partial blockage to the passage of food lead to symptoms similar to those of esophageal atresia, but surgical treatment may be unnecessary or delayed. In contrast to esophageal atresia which represents an acute problem, the stenoses are chronic disorders which are usually treated by dilation. The severity of symptoms, the duration of the disorder, and the number of therapeutic procedures vary, but in some cases it takes many years to restore such patients to health. Gross[93] mentions a boy who, during the first 8 years of life, was given 91 dilations, and adds that "the expense and the tribulations of hospitalization attendant to these were enormous." As is true of other types of malformations, congenital esophageal anomalies of mild degree contribute more to chronic illness than the severe forms which are often fatal or cured by surgery.

Congenital atresias of the intestine and colon result in death soon after birth unless surgical relief is given promptly. Although remarkable cures have been achieved in some of the cases, disappointments are not rare after successful operations. It happens many times that an infant operated upon for duodenal obstruction is recognized as a mongol after the bandages and therapeutic implements, which nowadays usually hide a surgical patient, are removed. Gross[93] found that seven of thirty-six infants kept alive by surgical relief of duodenal atresia or stenosis were later recognized as mongols. Some patients who are relieved of atresias in the lower intestinal tract by surgical measures may later suffer from chronic feeding difficulties, malnutrition, and recurrent attacks of obstruction caused by adhesions. *Congenital stenoses* of the intestine and colon often take a chronic course from the beginning. While severe forms cause symptoms indistinguishable from the atresias, milder forms are manifested by occasional vomiting or abdominal pain, retarded weight gain, and vague complaints, which are often treated for months or even years, by dietary measures, atropine, laxatives, or psychotherapy.

Similar conditions prevail in cases of *congenital intestinal malrotation* which are sometimes not recognized until later in life. Recurrent abdominal pain, nausea, vomiting, and symptoms resembling celiac disease characterize such cases which can now be recognized as developmental anomalies by roentgenologic examination. A mild form of anomalous intestinal fixation is the *mobile cecum*. This rather frequent anomaly may remain symptomless or lead to acute or chronic manifestations in children as well as in adults. The patients may suffer for many years from recurrent abdominal colics localized in the right lower quadrant or near the umbilicus. These painful attacks, often associated with nausea and mistaken for appendicitis, are due to torsion of the cecum. They may be relieved quickly by change of position and be of such short duration that the patients are often considered as neuropathic by those unfamiliar with the disease picture. Chronic constipation as well as diarrhea occur between the crises. Inflammatory processes may complicate the picture and further simulate chronic appendicitis. Recurrent vomiting and gastric symptoms appear as secondary symptoms.[116]

Meckel's diverticulum is a frequent anomaly which causes pathologic manifestations in some of its bearers. Symptoms usually appear early in life, but older children and adults may also be affected. Massive hemorrhage, intussusception, or a picture simulating acute appendicitis are the best-known manifestations of diverticulitis since they cause acute and dramatic incidents. However, peptic ulceration, intermittent obstructive phenomena, herniation, and recurrent pain may in some cases cause chronic disability or illness for many years.[30]

Congenital duplications of the alimentary tract are known under many different names. They often exist without causing symptoms or they may become suddenly noticeable by vomiting, hemorrhage, or signs of obstruction. Although symptoms occur characteristically in the early years of life, manifestations in older children and adults have been recorded. In some instances intestinal duplications cause protracted illness. Intermittent abdominal pain, rectal

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bleeding, and anemia may last for many years until the cause of the disturbances is discovered.[57,146] Duplications originating in the thorax usually described as *mediastinal cysts* may lead to pulmonary compression, stridor, and respiratory symptoms. Those lined by gastric mucosa are sometimes complicated by peptic ulceration and perforation which in turn may result in chronic lung disease, hemoptysis, or hematemesis. Such cysts are sometimes combined with malformations of the spine.[200] Duplications arising from the intestine but lying in the thorax may lead to compression of the heart and lung and cause cardiorespiratory symptoms; or, after ulceration, result in hemorrhages and anemia.[93]

In the condition called "*annular pancreas*" two processes of pancreatic tissue encircle the middle part of the duodenum, thus causing compression of the viscus. Many bearers of this malformation are symptomless during childhood but develop acute or chronic signs of duodenal obstruction in adult life. Epigastric pain, nausea, vomiting, and chronic malnutrition may result from this anomaly. In children annular pancreas is often combined with other congenital malformations such as intestinal malrotation, Meckel's diverticulum, esophageal atresia, congenital heart disease, or mongolism,[93] but patients with this pancreatic anomaly who reach adult life are usually free of serious associated defects. They are seldom diagnosed correctly, since their history, symptoms, and age are not characteristic of a congenital malformation. Peptic ulcer, jaundice, pancreatitis, or recurrent obstruction are the diagnoses which usually cover up the underlying anomaly.

Congenital megacolon (Hirschsprung's disease) is of particular interest in this discussion. The underlying congenital malformation is a microscopic one, namely absence of the parasympathetic ganglion cells of the intramural plexus in the rectum or the rectosigmoid. Clinical manifestations are seldom congenital but appear often during the first weeks of life. In other cases symptoms are noted later, when a chronic and obstinate constipation develops. Owing to the inability of the aganglionic segments to propel feces, stools may not be passed spontaneously for days or even weeks. The colon proximal to the aganglionic segments becomes tremendously distended by gas and fecal masses and the abdomen protrudes. Cathartics and enemas are constantly employed. Anorexia, lassitude, fetid odor of the breath, respiratory and circulatory difficulties, anemia, retarded growth, and malnutrition represent the chronic disease picture. The general emaciation and the contrasting marked enlargement of the abdomen characterize the disorder on external inspection. Before proper surgical treatment was practiced, these patients suffered for many years until inanition, intercurrent infection, or rupture of the distended colon resulted in death. Surgical removal of the narrow aganglionic segment, a procedure of relatively recent origin, results in relief and normal bowel habits.[93,189]

General *polyposis* occurs most often in the colon. This disorder is frequently dominantly inherited and it is likely that a congenital anomaly of the mucous membrane is present in affected persons. Symptoms may appear at any age after birth. In patients with polyposis, so many polyps may be present in the segment involved that the general character of the intestinal lining is altered and resection of the entire segment becomes necessary.[93] The most frequent mani-

festations are pain, rectal bleeding, and intussusception. Malignant degeneration is a further complication. Symptoms may last for many years, disabling the bearers of this anomaly to a great extent. Intestinal polyposis associated with melanin spots of the oral mucosa, lips, and digits[112] is a rare but very instructive syndrome. The pigmentations have been observed repeatedly at birth or in early infancy, and it may be assumed that the basic lesions of the intestine are also congenital. Dominant inheritance of the syndrome, which we may call "melanopolyposis," has been observed in several families. The pigmentations do not cause illness but serve as visible indicators of a syndrome of internal anomalies. The polyposis affects chiefly the small intestine, but the stomach and colon may also be involved. Abdominal pain, anorexia, nausea, diarrhea, constipation, intestinal bleeding, loss of weight, weakness, and anemia are clinical manifestations. Intussusception and bowel obstruction may occur in affected persons repeatedly. This broad spectrum of symptoms occurs not only in the patients but often in their relatives also. "Hereditary intussusception" has been observed in such families, a phenomenon which would be very puzzling without knowledge of the underlying syndrome.

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Congenital hernias cause a variety of chronic symptoms and disabilities. Some of them such as the inguinal hernias are easily diagnosed and are associated with well recognized disorders which need not be discussed here. Others are more concealed causes of illness and are usually detected with the help of x-rays. Large congenital diaphragmatic hernias are seldom compatible with life unless surgical closure of the defect is obtained in early infancy. It is the minor forms, the hiatus hernia and the retrosternal hernia, which cause delayed and chronic symptoms in older children and adults. Reflux of gastric juice into the esophagus produces esophagitis, dysphagia, hematemesis, or melena. Retrosternal hernias cause vague symptoms of low intensity related to compression of some intestinal segment.[93] Larger hernias which remain unoperated may produce thoracic symptoms such as dyspnea, cough, palpitation, or pain under the sternum. These complaints usually follow ingestion of meals or of large amounts of fluid. In the abdomen symptoms reminiscent of peptic ulcer or gall-bladder disease may persist. Nausea and vomiting are not rare. Intra-abdominal hernias often give rise to intermittent pain, nausea and vomiting until a crisis of intestinal obstruction leads to surgical intervention and recognition of the anomaly.

Cystic fibrosis of the pancreas is a congenital and hereditary disease which had not been generally recognized as an important cause of chronic illness of children before 1938.[8,26] This disorder, which is said to occur in about one per thousand of liveborn infants and in 2 per cent of all autopsied cases in children's hospitals, was obviously assigned to different diagnostic categories before its relatively recent recognition as an entity. The relationship of the pancreatic lesion to the pulmonary changes and to abnormalities of sweat are still under discussion,[108] but it is well established that a variety of symptoms of recurrent diseases must be attributed to this congenital disorder. It is instructive to consider in retrospect the diagnoses made in the past in cases now recognized as cystic fibrosis of the pancreas. Infants who inherit this anomaly may be born

with meconium ileus and symptoms of intestinal obstruction. Others show very slow weight gain after birth in spite of good appetite and large food consumption. Stools are bulky and sometimes frequent, foul, and fatty. These manifestations led to diagnoses of "chronic enteritis" or "disturbance of fat metabolism." When the food intake was restricted or the appetite declined because of pulmonary complications, "atrophy" or "malnutrition" were employed as labels for the disease. The chronic disease process of such children may be complicated by acute electrolyte disturbances which are due to anomalies of the sweat glands.[56] When death occurred it was ascribed to diarrhea or "toxicosis." In survivors, cough, wheezing, and dyspnea made their appearance, and "chronic pneumonia," whooping cough, asthma, emphysema, and even tuberculosis were diagnosed. If cor pulmonale complicated the lung disease[140] of a child with dyspnea and cyanosis, a diagnosis of "congenital heart disease" was often made. In some cases cirrhosis of the liver, ascites, edema, and "hemoptysis" appeared as terminal symptoms. One can hardly imagine the spectrum of clinical diagnoses employed to cover the manifestations of this congenital disorder. No other disease illustrates better the statement made above, that congenital anomalies are often diagnosed under the name of their complications, while the underlying disease goes unrecognized unless autopsy reveals its true nature.

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MALFORMATIONS OF THE UROGENITAL TRACT

Congenital malformations of the urogenital tract are among the most common anomalies of the human body. It is said that more than 10 per cent of all children are born with some urogenital anomaly. Some of these developmental errors cause early death, which explains their incidence being lower in the adult; others may remain entirely symptomless and go unnoticed throughout life. Between these two extremes are many which may cause acute or chronic illness at any age. Campbell[35] states that in children the majority of the causes of urinary obstruction and stasis are congenital in origin, and that over 90 per cent of the major pediatric urologic problems are due to a combination of obstructions and infections. If such anomalies are accompanied by external malformations of the genitalia, they are usually recognized at an early stage; if they are limited to internal structures, they are recognized only by adequate urologic examination or by autopsy. When the anomalies become a source of illness, they may cause urinary symptoms which facilitate an early diagnosis; but if they cause vague complaints only or manifestations referred to other organ systems, they may remain unrecognized for many years. Abdominal pains are still called "stomach aches" by the lay public, and even physicians refer them generally to the intestinal tract or the appendix. Only in recent years it has been recognized that a host of urinary tract anomalies may be the cause of "belly aches." Some of the urinary tract malformations are minor anatomic deviations from the normal but cause obstruction and stasis by their strategic location in the urinary path. By infection or back pressure they injure the kidneys seriously so that the damage is irreparable by the time they are diagnosed.

The diseases brought on by congenital malformations of the urinary tract illustrate well how in medical thinking the complications of a disorder are often

mistaken for the disease. Not many years ago urinary infections superimposed on obstructive malformations were diagnosed as "chronic pyelitis" or "chronic cystitis" and their treatment with disinfectants was generally accepted "malpractice." If pyuria was found in a case of unexplained fever, a satisfactory explanation had been found for the child's symptoms. But some of these cases proved intractable, ending in chronic and even fatal illness. Treatment of the superimposed infection did not remove the underlying obstruction, and stasis combined with recurrent bacterial invasions destroyed the renal tissue and led to renal failure. At autopsy, complications such as cystitis, pyelonephritis, stone, or hydronephrosis often dominated the disease picture so much that the causative malformation had become unrecognizable.

Urography, cystoscopy, ureteral catheterization, and retrograde pyelography have made possible early recognition of congenital malformations of the urinary tract which not long ago could not be detected by inspection, palpation, and examination of the urine. Modern instruments permit examination of the male as well as the female newborn child, thus making possible an early diagnosis of congenital defects. It is instructive to look back and to remember the disease pictures and diagnoses which masked these malformations before modern urologic examination was available. It is also worth remembering that even today many types of chronic illness of the urinary tract are still treated symptomatically without benefit of urologic diagnosis. The diagnosis of pyuria may cover many anomalies causing temporary or chronic obstruction and urinary stasis. Pyuria is found in renal disorders such as congenital solitary kidney, double kidneys, pelvic reduplication, ectopic kidneys, congenital cystic disease, and other developmental defects of this organ. It may also be the manifestation of ureteral reduplication, ectopy, stricture, idiopathic enlargement (megaloureter), and of aberrant renal vessels. Anomalies of the vesical outlet, valves of the posterior urethra, hypertrophy of the verumontanum, or meatal urethral strictures of prenatal origin result in urinary changes which may lead to the diagnosis of "pyelitis" or "cystitis," the complication being mistaken for the cause of the disease. In other cases of the same malformations, hematuria may be the presenting symptom and anemia an outstanding result. Treatment of such symptoms often gives the patient temporary relief but permits continuation of renal destruction by the obstructive malformation. Anomalies such as horseshoe kidney, ectopic kidney, or ureteral strictures, causing urinary stasis and infection predispose to stone formation. Removal of the stone removes a symptom but not the causative obstacle. Structural anomalies resulting in infection and stone formation cause pain which may be localized in the loin or back and thus contribute to the recognition of the underlying malformation. In other cases, children may complain for years of abdominal pain localized in the region of the stomach, umbilicus, or appendix although the cause of their pain is in the urinary tract. It is not rare that appendectomy is performed in children whose pain stems from ureteral strictures, anomalies of renal vessels or valves of the posterior urethra.[35] In other instances of urinary tract anomalies, gastrointestinal symptoms dominate the disease picture. Anorexia, nausea, vomiting, and loss of weight may be the chief complaints in obstruction due to anomalous renal vessels, urethral valves, hypertrophy of the verumon-

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tanum, or meatal stricture. Chronic constipation is a symptom in horseshoe kidney, ectopic kidney, ureteral strictures, urethral valves, and other anomalies of the urinary tract. Inability to gain weight may persist for years in patients with valves of the posterior urethra and lead to a deplorable state of "malnutrition." It is an unforgettable experience to see a child, emaciated like a victim of starvation, return to a normal nutritional state after surgical removal of an obstacle to urinary flow.

In some patients the recognition of obstructive uropathy is delayed because the urine is found to be normal on routine examination and the renal anomalies are masked entirely by symptoms manifested by other organ systems. In others the late results of renal destruction are recognized rather than the congenital cause of obstruction. Bilateral renal hypoplasia, polycystic disease, ureteral strictures, megaloureter, valves of the posterior urethra, and other congenital malformations are sometimes overlooked while their renal complications are recognized, investigated, and mistaken for the basic disease.[35] Many cases of "chronic nephritis," "chronic interstitial nephritis," or "nephrosclerosis" of childhood are the end result of congenital uropathies, but the postnatal complications overshadow the underlying malformations. Polyuria, polydipsia, headaches, vomiting, disturbance of vision, anemia, cardiac enlargement, hypertension, convulsions, and uremia may dominate the clinical picture.

In some cases *renal dwarfism* or renal hyperparathyroidism with osteitis fibrosa cystica (renal rickets) develop. The urine shows low specific gravity, some albumin, casts, and pus cells. The nonprotein nitrogen of the blood is elevated, and a diagnosis of "chronic nephritis" is often made.

Mitchell[144] emphasized as early as 1930 that heredity plays an important role in the etiology of "*nephrosclerosis*" in childhood, that many cases are congenital, and that obstruction of the urinary tract is often present. Clark[39] observed a family in which two members developed chronic renal failure in infancy and a third died at an early age and was found to have a hypoplastic horseshoe kidney.

A hereditary tendency to "chronic nephritis" of adults has been observed in many families, and in 1950 Hawkins[98] described a *hereditary renal dysplasia* which is of special interest in this review. This renal disturbance resembles closely acquired chronic glomerular nephritis clinically as well as anatomically, but it takes a relatively benign course. Although abnormal urinary findings are often present in infancy and early childhood, signs of renal failure may not appear before the fifth decade. That this renal dysplasia is a congenital anomaly is suggested by the fact that it is accompanied by other developmental anomalies. Iliac horns, arthrodysplasia of the elbow joints, rudimentary patellae, and dysplasia of the nails are found in this syndrome, which is apparently inherited as a dominant trait.

A prenatal factor in chronic *interstitial pyelonephritis* is suggested in a family in which this disorder occurred in a hereditary form. In this kindred described by Perkoff and co-workers,[157] fifty members had renal disease with the characteristics of interstitial pyelonephritis, but progressive renal insufficiency developed only in the males. No gross renal malformations were observed and the inherited susceptibility has not been explained. A histologic renal anomaly or

abnormal lymphatic connections between the colon and the kidneys may be the inherited trait which predisposes to infections.

In recent years an interesting group of metabolic disturbances has been referred to *congenital functional defects of the renal tubules.*[110] A nephrogenic diabetes insipidus insensitive to pitressin has been repeatedly observed,[47,205] and Williams and Henry[217] detected this defect in seven members of one family, in which it was inherited as a sex-linked recessive trait. Erratic fever, vomiting, constipation, dehydration, malnutrition, and hyperelectrolytemia are clinical manifestations. Vitamin-D resistant rickets, often inherited as a dominant trait, has been attributed to a tubular inability to reabsorb phosphate.[71,131] Renal glycosuria or renal diabetes is often transmitted as a dominant characteristic. In Wilson's disease or hepatolenticular degeneration amino-aciduria due to inability to reabsorb amino acids[199] has been observed (p. 89). Renal hyperchloremic acidosis[34] has been explained as a tubular defect of bicarbonate reabsorption.[122] Polyuria, polydipsia, nephrocalcinosis, pyuria, renal stones, rickets, and stunted growth are the clinical symptoms of this tubular anomaly which may occur as a hereditary trait.[173] A group of metabolic disturbances, often referred to as the "Fanconi syndrome" and characterized by amino-aciduria, phosphaturia, glycosuria, and sometimes associated with cystinuria and cystinosis is complex in origin, but the majority of authors[70,131,186] are of the opinion that the primary cause of this disorder lies within the renal tubules. Clay, Darmady, and Hawkins[40] found in two dissected cases congenital malformations of the renal tubules. The proximal convoluted tubules were abnormally thin and presented a "swan-neck" appearance. The clinical manifestations are attributed by some investigators to faulty phosphorylation of glucose and amino acids and to inability of the kidneys to retain phosphorous, calcium, and sugar. Other students of this disease consider an inborn error of cystine metabolism as the primary defect and the renal lesions as the result.[79] Clinical manifestations are rickets or osteomalacia, multiple fractures, wasting, polyphagia, polyuria, and cirrhosis of the liver. It is now well established that several microscopic or functional congenital anomalies of the renal tubules are responsible for many metabolic disorders which make their first appearance during childhood or in later life in the form of a variety of clinical symptoms.

In children, approximately 20 per cent of all *neoplasms* begin in the kidney. With few exceptions all of these are embryomas of the kidney or Wilm's tumors. These tumors are congenital, mixed tumors which arise from the renal anlage.[49] The average age of clinical manifestations is about 3 years. While the tumors are only rarely present at birth, their precursors consisting of undifferentiated metanephric tissue can be found in the neonatal period.[161] Hamartomas may occur in the renal medulla and contain connective tissue, smooth muscle, and fat. They as well as the renal tumors found in patients with tuberous sclerosis represent developmental anomalies.

MALFORMATIONS OF THE SKIN

Malformations of the skin are too numerous to be discussed here in detail. It will be possible only to mention those conditions which either cause chronic illness or accompany malformations of other organs thus forming morbid syndromes.

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Pigmented nevi are often present at birth and some of them appear soon after birth. Intraepidermal and junctional nevi are of importance because they are, in some instances, potentially malignant. The most common nevi are intradermally situated and usually benign. Pigmented, hairy, and warty nevi may cover large areas of the skin and disfigure the patients seriously. The nevus pigmentosus et pilosus which resembles an animal fur to some extent may be so repulsive to lay persons that affected children are often excluded from normal activities and regular schooling.

A *syndrome of congenital pigmentations* of the skin, sexual precocity, and polyostotic fibrous dysplasia is mentioned on page 80. *Pigmentations of the lip*, of the oral mucosa and the fingers occur in persons with intestinal polyposis (p. 69). *Incontinentia pigmenti* is sometimes present at birth or develops in early postnatal life. The pigment changes may be preceded by inflammatory lesions of various kinds. This anomaly is characterized by irregularly shaped pigmented areas, which are connected with each other by dendritic processes, thus forming a network on the skin. The pigment migrates from the epidermis into the cutis where it is found in the papillae or near blood vessels. Several stages and various types of the disorder have been observed.[78] The condition is rare but noteworthy because of its association with disorders such as dwarfism, microcephaly, ectodermal dysplasia, dental defects, ocular anomalies, paraplegia, and others.

Vascular nevi affect most often the skin or mucous membranes. Some of them are harmless, others present cosmetic problems. Cavernous angiomas are disfiguring and cause bleeding by trauma or ulceration. *Nevus flammeus* or port-wine nevus represents a serious problem when occurring on the face. It is difficult to treat and may be indicative of cerebral involvement. Some patients have a unilateral port-wine nevus extending over the facial areas supplied by the branches of the trigeminal nerve. Corresponding to the extent of the nevus there occur angiomatous formations of the meninges and calcifications of the brain substance. Such patients have glaucoma on the affected side, petit mal attacks, migraine, convulsions, and mental deficiency (Sturge-Weber syndrome). *Congenital telangiectases* represent dilated capillaries usually found on the face and neck. The condition which may be hereditary is rather harmless and does not result in hemorrhages from the mucous membranes.

Cutaneous hereditary hemorrhagic telangiectases are of greater medical importance since they are indicative of similar lesions on the mucous membranes of the nasal septum and of the intestinal and urogenital tracts. In mild cases hemorrhages are absent, but in some persons severe bleeding may occur from internal organs. An interesting association of these telangiectases are arteriovenous fistulas of the lungs which, though congenital, cause serious symptoms in later life[194] (p. 64). Such telangiectases are dominantly inherited, but hemorrhagic manifestations vary greatly in members of affected families.

Hereditary lymphedema (Milroy's disease) occurs in the lower extremities. The condition occurs unilaterally or on both legs; it may involve the ankles only or extend to the knee or hip joints. This disorder is sometimes inherited as a dominant trait, but not all hereditary cases are congenital; it may be asympto-

matic in some cases, yet disfiguring and painful in others. Associated congenital malformations have been observed in some instances.[134]

Ichthyosis simplex appears as a rule in the early months of infancy and increases in severity during childhood. The abnormality consists in thickening of the horny layer of the epidermis and underdevelopment of the stratum granulosum, hair follicles, and sebaceous glands. The dry and scaly skin appears often dirty and represents a cosmetic problem. Dominant inheritance is the rule, but irregular transmission is frequent, since the expression of the abnormal trait varies greatly. Localized and generalized forms may alternate[46] in pedigrees. Some forms are combined with dental or osseous anomalies, mental deficiency, nervous or ocular disorders.[134] A sex-linked recessive form affecting only males, and transmitted by apparently normal females, has been described as ichthyosis vulgaris.[41]

Ichthyosis fetalis (Harlequin fetus) can be omitted from this discussion because it is lethal, but the closely related ichthyosis congenita is compatible with life. The viable forms present serious feeding and nursing difficulties. In addition to the disfiguring cutaneous changes, the eyes may be damaged by ectropion, corneal ulcerations, and opacities. Deafness, malformations of the ear, and disturbances of perspiration sometimes accompany the skin lesions. It seems that this serious ichthyosis is determined by a recessive gene which is present in apparently normal parents.

Xeroderma pigmentosum appears in most cases soon after birth in the form of red areas which soon develop hyperpigmentation, atrophy, and telangiectases. In addition, intense photophobia, corneal and cutaneous ulceration, warty growths, scars, and epitheliomas make their appearance. This very disabling disorder leads to death, as a rule, before adulthood is reached. Since the disease is due to recessive inheritance, more than one sibling of a family may be affected. The inherited susceptibility of the skin is aggravated by sunlight and exposed areas are most affected. Mental deficiency, retarded growth, and deafness are sometimes accompanying defects.[41]

Anhidrotic ectodermal dysplasia is characterized by a white and thin skin, absence of sweat glands, defective sebaceous glands, pale and scanty hair, partial or complete lack of teeth, atrophic rhinitis, pharyngitis and laryngitis, and intolerance to heat. The patients are often small and delicate, and have a depressed nasal bridge, thick lips, and maxillary hypoplasia. Mental deficiency, though not always present, has been reported in many cases.[211] This severe form of ectodermal dysplasia is inherited as a sex-linked recessive trait. Affected persons have not only many cosmetic problems, but they are in hot weather also handicapped by dyspnea, fever, or convulsions. The chronic rhinitis leads to destruction of the nasal bones and to loss of the sense of smell.[41] In the *Ellis-van Creveld syndrome* ectodermal dysplasia is combined with polydactyly, vitium cordis, and nail defects. In this syndrome, which is inherited as a recessive trait, the sweat glands are functioning normally.[62] There is also a milder dominant type of ectodermal dysplasia which may be indistinguishable clinically from the sex-linked recessive form. As a rule, only the male patients show the fully-developed syndrome while the females have the defect in an attenuated

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form. Ectodermal dysplasia has been observed in combination with microphthalmus and hydrocephalus.[41]

Epidermolysis bullosa occurs in many degrees, all characterized by a tendency to form blisters spontaneously or in response to minimal traumas. In the severe "dystrophic" form, the bullae appearing on the skin and mucous membranes are deeply situated and leave scars after healing. There is a recessively inherited type which often shows severe congenital lesions consisting of skin defects, adhesions, blood-filled bullae, and nail defects. The mucous membranes are also affected, causing ulcerations in the nasal cavity, chronic bronchitis, or laryngeal stenosis. As the children grow up, their teeth are small, deficient in number, and irregularly implanted. Growth is delayed and many patients are undersized, and some mentally retarded. The skin lesions are often the seat of secondary infections leading to scars and contractions. The fingers and toes may become fused in flexion.[133] In some patients the conjunctivae are involved and corneal opacities impair vision. The disorder is always incapacitating in its severe form and some of the cases are unviable. Epidermolysis bullosa simplex, which is inherited as a dominant, takes a milder course. The patients are of normal body build and their teeth and nails are normal. The blisters are superficial, leave no scars, and appear only in areas exposed to trauma, such as the feet and hands. The tendency to formation of blisters is aggravated by summer heat. This form of the disease is not rare in certain areas of the South.[153] It causes disability in manual laborers and in persons walking great distances.

Cutis laxa (Ehler-Danlos syndrome) is a condition which permits a remarkable stretching of the skin with spontaneous return to its original position. The skin is thin and fragile, the elastic fibers are well developed, but the subcutaneous tissue is lacking. Skin of this type is easily injured by slight traumas resulting in tears, ecchymoses, ulcerations, and linear scars. Marked laxity of the joints is always present. In some of the cases, pseudomolluscoid tumors, lipomas, acrocyanosis, and dental and osseous anomalies were observed. The laxity of the joints and muscular weakness cause orthopedic problems such as dislocations, disturbances of gait, and deformities. Dominant inheritance has been reported but sporadic cases appear to be more numerous.[114]

Recklinghausen's neurofibromatosis is a hamartosis with protean manifestations. The skin lesions present cosmetic problems but they are also important as external indicators of the underlying disease. Pigmentations in the form of café-au-lait spots, soft cutaneous tumors, and tumors of the peripheral nerve are outstanding symptoms. Osteoporosis and cystic bone changes, scoliosis, osseous overgrowth, endocrine disorders, pheochromocytoma, tumors of the central nervous system and of the cranial and spinal nerves, tumors of the gastrointestinal tract, and terminal sarcomas have been repeatedly observed. Cutaneous pigmentations and elephantiasis neuromatosa may be congenital, but many of the other symptoms appear in later years. Mental deficiency or mental imbalance is not rare. Dominant inheritance is the rule, but sporadic cases do occur.[41]

Tuberous sclerosis represents another hamartosis which manifests itself in many organs. Adenoma sebaceum, consisting of hypertrophic sebaceous glands

and angiomatous proliferations, is the best-known skin manifestation of the disorder. Mental retardation and epilepsy are additional symptoms. Cystlike lesions and periosteal thickening of tubular bones and calcifications of the brain may be seen in roentgenograms. Multiple cerebral tumors consisting of glial fibers, retinal tumors, subungual fibromas, rhabdomyomas of the heart, and renal tumors may be found. Numerous small cysts develop sometimes in the lungs causing dyspnea, pneumothorax, and heart failure.[51] Most of these manifestations appear in older children or adults, but convulsions, cerebral calcifications, cardiac rhabdomyoma, and retarded mental development have been observed in infants with this disease.[52] Dominant inheritance can be demonstrated in many pedigrees, but the intensity and expression of the disease may vary in affected members.

ENDOCRINE DISORDERS

Disorders of the endocrine glands have assumed a special position in medical thinking. When a patient's disease picture can be referred to dysfunction of an endocrine gland, the etiology of the disease is considered adequately "explained" in most of the cases and there is relatively little interest in the causes of the endocrine deficiency. It is frequently overlooked, therefore, that many endocrine disorders, particularly those of children, are due to congenital malformations of the glands or to malformation of surrounding structures. It is more difficult to demonstrate prenatal etiological factors in endocrine disturbances of adults, but indirect evidence indicates in many cases that even in glandular disturbances beginning in adulthood a congenital anomaly may play a leading role.

Hypothyroidism of children is due to a congenital defect in most of the cases. Wilkins[216] estimates that about four-fifths of the patients with hypothyroidism in childhood show evidence of congenital deficiency. The most common form of this defect is represented in this country by sporadic cretinism, which is due to a congenital malformation of the thyroid gland. This gland, which normally arises as a diverticulum from the pharyngeal floor, may fail to develop entirely or may be formed as a rudiment only. The cause of this developmental defect is unknown. The anomaly occurs, as a rule, only once in a family and only one of monozygotic twins may be affected.[209] A different form of cretinism is attributed to an *inborn error of metabolism*. Patients of this type have goiters although they live in nonendemic areas and receive a sufficient supply of iodine in their diet.[97] Several children may be affected in one family[107,125,182] and it appears likely that the metabolic deficiency is inherited as a recessive Mendelian trait. The thyroid deficiency is due in such cases to an inability of the gland to produce an effective thyroid hormone in sufficient amounts.[107] *Endemic cretinism* represents a different type of congenital thyroid deficiency. This form occurs in areas of endemic goiter and is, therefore, attributed to iodine deficiency and possibly other nutritional factors. The mothers of endemic cretins always have goiters, and the children are born, as a rule, with enlarged thyroid glands. Older cretins may have goiters or secondary atrophy of the thyroid gland. The mental deficiency and deaf-mutism characteristic of endemic cretinism date back to intrauterine life. Although endemic cretinism has not been observed in recent

years in the United States, it is still existent in remote areas of many countries. In endemic regions this type of cretinism is so frequent that it represents a serious social and economic problem to the entire population. By improvement of the maternal diet, particularly by incorporation of iodine in the salt, an endemia of cretinism can be wiped out within a few decades.[61]

Hyperthyroidism is much rarer in children then hypothyroidism. This disorder is not congenital but prenatal factors can be demonstrated in cases with a hereditary tendency. In some families the thyroid disorder occurs in several members and through several generations; in other families one observes an accumulation of endocrine disturbances such as hyperthyroidism, diabetes insipidus, obesity, or diabetes mellitus,[13,210] which cannot be considered as accidental. Whether such pluriglandular manifestations in families can be explained by inherited anomalies of the pituitary gland or of the hypothalamus has not been decided.

Congenital defects in the pituitary-hypothalamic area are responsible for a variety of endocrine manifestations. *Pituitary dwarfs* usually appear normal at birth, but after several years stunting of growth becomes apparent. The disease picture is not always clearly circumscribed, and differentiation from other forms of dwarfism is sometimes difficult. In some of the cases, slowly growing cysts (Rathke pouch cysts) or craniopharyngiomas developing near the pituitary account for the lack of growth. In others, gross pathologic lesions cannot be demonstrated and an inherited pituitary hypoplasia must be assumed. A number of pedigrees have been collected[168] which indicate that pituitary dwarfism can be transmitted by a recessive gene. Since human pedigrees are often too small for genetic investigation, the role of heredity cannot always be demonstrated. Pituitary dwarfism occurring in certain strains of mice[94] shows definite analogies to human conditions. It is inherited as a recessive character and attributable to an anomaly of the anterior lobe. Like human pituitary dwarfs, mouse dwarfs appear normal at birth but lag in growth subsequently. Their ossification is retarded and they remain sterile.

The true *Froehlich's syndrome* consists of retardation of sexual development and obesity. It was caused in Froehlich's original case[31] by a cystic growth in the pituitary region which proved to be operable. Craniopharyngiomas and developmental anomalies have been repeatedly discovered in autopsied cases of hypogonadism. Some of these cases show also obesity and diabetes insipidus.

Congenital defects of the hypothalamus may result in endocrine disturbances. It is known that obesity can be produced experimentally by hypothalamic injury and tumors affecting this area may cause similar effects. Among these hamartomas, craniopharyngiomas and angiomas can be traced to embryonic maldevelopment. A child with Cushing's syndrome has been described who had a malformation in the tuberoinfundibular region.[201] The tuber cinereum contained mostly glia and the nuclei of the area were poor in nerve cells. It should be emphasized that this malformation was not recognizable macroscopically but was revealed in serial sections. In the Laurence-Moon-Biedl syndrome, obesity is associated with hypogenitalism, mental deficiency, retinitis pigmentosa, and polydactylism. The syndrome is inherited as a recessive or incom-

pletely dominant character[83] but only polydactylism is recognizable at birth. The obesity which is attributed in these cases to a developmental anomaly of the hypothalamus, makes its appearance within the first few years of life. In one case[19] the anomalies of the syndrome were associated with a tumor of the infundibulum.

No anatomical substrate has as yet been found for the most frequent form of *juvenile obesity*, which is a benign anomaly of development of adolescence tending to spontaneous regression. Since neither a thyroid nor a pituitary defect can be demonstrated in this type, "overeating" or psychogenic factors has had to take the blame for the condition in recent years. While these and other postnatal factors play a role in the etiology of obesity of adolescence, a "constitutional" predisposition cannot be denied. Family histories reveal a higher incidence of obesity and diabetes among relatives of obese children than in those of controls.[216] The accumulation of obese people in pedigrees cannot be simply explained by similar food habits, since the obese members are sometimes not found in the same family unit, but in different generations and different households. In the same family and under similar living conditions an obese child may grow up together with slender siblings. These obese children have many features in common. They are taller, as a rule, than their coevals and the entire skeleton as well as the internal organs show an overgrowth. The facial features are frequently fine, the hands small and the fingers tapering. Maturation is usually normal in girls, but sex development is often delayed in boys. These additional characteristics of obese children cannot be explained by overeating alone. Although the morphologic substrate of this, usually temporary, abnormal pattern of adolescence has not yet been recognized, an inherited anomaly must be assumed in most of the cases. It is of interest that a strain of mice exists in which obesity of severe degree is inherited as a recessive character. The obese homozygous mice are sterile and the condition is propagated by heterozygous animals of the strain.[141] While the food consumption of the obese mice is much larger than that of their normal littermates, the drive to overeating cannot be explained on "psychological" grounds, but rather by an inherited pathologic mechanism which still needs elucidation.

Precocious puberty due to congenital malformations of the hypothalamus has been repeatedly observed.[12,29] In some of the cases autopsy has revealed small hyperplastic malformations in the region of the corpora mammillaria or of the tuber cinereum. In one instance an astrocytic hamartoma represented an intermediary stage of malformation to tumor formation.[92] Neurofibromatosis or tuberous sclerosis affecting the hypothalamic region and causing precocious puberty represent specific forms of developmental hamartoses. Teratomas, dermoid cysts and pinealomas arising from the pineal region and affecting the hypothalamic area may induce precocious puberty in boys. The syndrome of precocious puberty, skin pigmentation, and fibrous dysplasia of bone[3,132] represents a combination of developmental defects of unknown origin. Since the skin pigmentations are usually present at birth, a prenatal determination of the syndrome has been assumed. In idiopathic or constitutional sexual precocity no pathologic findings have as yet been discovered in the brain or in the endocrine

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system. Yet several pedigrees of precocious puberty in boys have been reported. Jacobsen and Macklin[111] investigated a family in which 27 males were affected with precocious sexual and somatic development.

Hypogonadism also may result from malformations of the pituitary-hypothalamic area. In an autopsied case of pituitary dwarfism and hypogonadism[9] separation of the neuro- and adenohypophysis could be recognized. This dystrophy, which dated back to early embryonic life, led to the formation of a craniopharyngioma. Without causing tumor symptoms, the craniopharyngioma regressed, but scar tissue was formed which separated the adeno- and neurohypophyses completely. This case indicates that an embryonic anomaly may undergo in postnatal life a variety of changes which, at the time of autopsy, may mask the original malformation. Thus craniopharyngioma, pinealoma, infundibuloma, cysts, and other tumors derived from embryonic residues[86] are often held responsible for hypogonadism,[12] while the underlying congenital malformation escapes attention.

Similar considerations apply to many cases of *diabetes insipidus*. This anomaly of water metabolism may be due to a lack of pitressin or to an anomaly of the renal tubules (p. 74). The pitressin deficiency is caused by defects of the hypothalamus or of the neurohypophysis. Heredity plays a role in some of the cases. In a pedigree observed by Adolf and Alfred Weil[212] diabetes insipidus could be traced through five generations as a dominant trait. It was suggested that a hereditary abnormality of the brain may account for the transmission of this disorder. This assumption is supported by the fact that in some hereditary cases diabetes insipidus is associated with mental deficiency and other congenital defects.[206] Diabetes insipidus is also found in some patients with the Laurence-Moon-Biedl syndrome (p. 79). Heredity cannot be demonstrated in all cases of diabetes insipidus and sporadic cases occur often.

Turner's syndrome is usually considered an endocrine disorder, since it has been investigated chiefly by endocrinologists.[196,215] It is diagnosed, as a rule, in young girls with sexual infantilism and short stature. They show symptoms of estrogen insufficiency but an increase of gonadotropin production. On exploratory laparotomy, infantile, normally formed tubes and uteri are found, but the gonads are represented merely by narrow white bands in the ligamentum latum. Although these gonads are usually described as ovaries, they show so little differentiation that the true sex of the patient may be in doubt.[159] This developmental anomaly is associated, as a rule, with other congenital malformations such as pterygium colli, anomalies of the spinal colum, cubitus valgus, coarctation of the aorta, congenital heart disease, eye defects, and others. The stunted growth and the congenital malformations cannot be explained on an endocrine basis, but the endocrine symptoms are obviously a part of a general and early embryonic disturbance. Recently it has been shown that genetically male persons may show the same syndrome. Owing to the absence of differentiated testicular tissue, they develop female sex organs.

Male hypogonadism is sometimes caused by congenital absence (anorchism) or congenital atrophy of the testes. *Cryptorchidism* may be transitory or permanent; it may be associated with endocrine disturbances or occur in indivuduals

without such signs; but it is always a congenital anomaly since descent of the testes into the scrotum takes place normally in the eighth or ninth month of fetal life. In cryptorchidism the testis may be retained in the abdomen, above the internal inguinal canal, in the canal, or it may pass the external ring but be displaced into the femoral, pelvic, or pubic area.

With the exception of sex reversal caused by hormone-producing tumors, all forms of *hermaphroditism* and *pseudohermaphroditism* are congenital malformations. Even the tumors which produce heterosexual hormones and bring about sex reversal in adult life are attributable to fetal tissue remnants and can be considered as developmental errors.[172] In the case of congenital adrenal hyperplasia of females, excessive androgen production results in a form of pseudohermaphroditism. Such girls have normal female internal sex organs with the exception of the termination of the genital duct which is in the urethra. The external genitalia resemble the male organs to some extent. The deviation from normal sex development probably occurs between the fourth and fifth month of fetal life. Boys with congenital adrenal hyperplasia usually have normal external genitalia at birth, or the penis may be enlarged. Their adrenal anomaly which also results in increased androgen production does not lead to any heterosexual development but to precocious maturation. In addition, Addisonian crises occur rather frequently. They often go unrecognized representing a picture of severe gastrointestinal disturbance and dehydration. Male and female children affected with this type of congenital adrenal hyperplasia have been repeatedly observed in the same family. A nonadrenal type of female pseudohermaphroditism occurs in girls with multiple congenital malformations of the genitourinary tract.[156,210] These patients have no signs of excessive androgen production, but anomalies of the kidneys are often associated with those of the external genitalia. A corresponding type of pseudohermaphroditism exists in males. Such patients have testes and normal adrenals, but various abnormalities of the genital ducts and external genitalia. True hermaphroditism is characterized by the presence of testicular and ovarian tissue in the same person. Such intersexes may be bilateral, having an ovotestis on each side; or unilateral having an ovotestis on one side; or lateral (alternating), having a testis on one side and an ovary on the other side.[101] These deviations from the normal development of the gonads date back to the ninth week of intrauterine life.

Addison's disease or chronic adrenal insufficiency was originally considered a complication of tuberculosis. As this infection becomes rarer, other etiological factors are being recognized. Addisonian crises in boys with congenital adrenal hyperplasia have been mentioned before. Atrophy of the adrenal glands attributed to faulty embryonic development has been described by Crosby.[44] Another form of idiopathic Addison's disease not associated with tuberculosis is related to idiopathic hypoparathyroidism. The two forms of glandular insufficiency may occur in the same patient[124] or they may appear alternately in the same family.[210] Although moniliasis and other infectious agents have been considered as etiological factors, the possibility of an inborn weakness of the adrenal and parathyroid glands must be considered in such cases. Several instances of idiopathic hypoparathyroidism occurring in childhood showed a

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familial incidence and association with other congenital malformations.[121] Mitchell[145] observed chronic hypoparathyroidism associated with a multicystic kidney in a child whose mother developed a parathyroid adenoma. Chronic hypocalcemia and tetany have been found in association with congenital malformations of the brain.[152] Such observations point to the possibility of a prenatal origin of idiopathic hypoparathyroidism of childhood.

Pseudohypoparathyroidism (Seabright-Bantam syndrome)[4] resembles hypoparathyroidism clinically and biochemically, but fails to respond to administration of parathormone. The metabolic manifestations of this syndrome are attributed to an inability of the renal tubules to respond to parathormone by phosphorus reabsorption. The renal anomaly is associated with other congenital malformations such as dwarfism, mental deficiency, shortness of metacarpal bones, and dyschondroplasia. The repeated occurrence in families and in pairs of monozygotic twins point to a genetic determination of this syndrome.[33]

A rare but interesting *pluriglandular syndrome* consists in adenomatosis of the anterior pituitary, the parathyroids, and the pancreatic islands. The clinical symptoms vary; but hypoglycemia, hypogonadism, and ulcers in the gastrointestinal tract have been repeatedly observed. Several cases occurred in one family and in two generations. No lesion has been discovered which could be considered as a common cause of such multiple manifestations and the syndrome has been attributed to a dominant gene with pleiotropic effects.[214]

MALFORMATIONS AND DEFECTS OF THE BLOOD

Congenital anomalies of the blood belong in the class of histologic malformations. Blood is a mesodermal tissue composed of corpuscular elements and plasma. "Biopsies" of this tissue are easily performed, and blood counts, aided by marrow punctures, have become routine procedures of medical examination. This fact explains that hematology has developed into a science of its own, but it was only recently that some of the congenital defects of the blood were recognized as malformations. Heredity plays an important role in the etiology of congenital anomalies of the blood, but sporadic defects are also encountered. There exist probably many genetically determined variations of the blood elements. Some of them are well tolerated and not pathogenic. Only a few representative conditions will be cited in this context.

Some of the anomalies of the blood parallel gross congenital malformations. Others occur in persons who appear normal at birth, but show, on microscopic examination, congenital deformities of the corpuscular elements of the blood. Finally, there exist chemical congenital defects leading to chronic illness which represent a transition to the inborn errors of metabolism.

Panmyelophthisis (aplastic or hypoplastic idiopathic anemia) was first described by Fanconi.[69] Although a rare blood dyscrasia, it illustrates well the fact that hematic malformations parallel those of the skeleton and other organs. This anemia is seldom recognized at birth, although it has been described in infancy.[14] As a rule, it takes several years before anemia and hemorrhages reveal the anomaly of the blood. Affected children appear tired and retarded in growth. The disorder is a chronic one; it extends over several years, is inter-

rupted by periods of spontaneous improvement but ends fatally. The underlying anomaly is a replacement of the bone marrow by fat marrow. A hyperchromic anemia resistant to therapy develops. Granulocytopenia, absolute lymphopenia, and thrombopenia are additional findings. The blood dyscrasia is accompanied by multiple congenital malformations. Microcephaly, absence or anomalies of the thumbs and radius, atresia of the auditory meatus, anomalies of the urinary tract, testicular hypoplasia, clubfoot, and other congenital developmental defects occur in many patients. This association indicates that the syndrome is of prenatal origin. In addition there are abnormal pigmentations of the skin, mental deficiency, and deafness. Such cases have been repeatedly observed in siblings whose parents were free of the disease. It is assumed that the syndrome is a recessive, hereditary trait.

Benjamin's anemia is a congenital hypoplastic anemia which affects erythropoesis without disturbance of the white cells and thrombocytes. Affected infants show epicanthic folds, congenital malformations of the heart and of the genitalia, and physical and mental retardation.[63] Familial hypoplastic anemias are not always accompanied by gross defects and they may be observed in children who do not have associated congenital malformations.[64] Comparable forms of congenital anemias appear sporadically without a demonstrable genetic background. Smith,[180] reviewing the aplastic and hypoplastic anemias of infancy, concluded that "pure red-cell anemia and related hypoplastic anemias represent examples of congenital hematopoietic anomalies comparable to other somatic malformations originating from disturbances in embryonic and fetal life."

Osteopetrosis (Albers-Schoenberg's disease, marble bone disease) is a deforming osseous anomaly (p. 60) that involves the blood system by sclerosis of the bone marrow. Hypochromic anemia develops and nucleated red cells appear in the peripheral blood. Aplastic anemia may be a terminal feature of this syndrome which, in its typical form, is inherited as a recessive trait.

Spherocytosis (congenital hemolytic anemia) is a hereditary and congenital malformation of red blood cells which undergo excessive destruction, leading to a chronic hemolytic anemia. During crises fever, jaundice, abdominal pain, and pallor cause acute illness. Infants with spherocytosis may in rare instances develop anemia, jaundice, and even kernicterus in the neonatal period, but, as a rule, jaundice is seen in older children only. There are wide variations in the clinical picture of spherocytosis. Some affected persons remain free of clinical manifestations, while others suffer from many complications. Among these may be obstruction of the biliary tracts, gallstones, ulcerations on the lower leg, corneal opacities, and optic atrophy.[151] Stunted growth and secondary osseous malformations develop in some instances. Without proper treatment chronic invalidism or even death can result from complications. Removal of the spleen ameliorates the hemolytic process and the clinical course without change of the cellular defect. Spherocytosis is a dominantly inherited trait, which in itself is not a disease, but may cause illness in the presence of accessory factors. It is not known whether such accessory factors are genetic or environmental, but it is known that removal of the spleen, a "nongenetic factor," can enable affected persons to live a normal, healthy, and useful life. *Ovalocytosis* is a comparable

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congenital anomaly of the red cells inherited as a dominant trait. It may be well tolerated or result in anemia, gallstones, and splenomegaly.[218] *Acanthrocytosis* is a rare erythrocytic malformation characterized by red cells with protoplasmic projections of various sizes. This rare anomaly may be associated with a celiac syndrome, spinocerebellar disturbances, and retinitis pigmentosa. The syndrome is apparently due to a recessive gene.[179]

Thalassemia (Cooley's or Mediterranean anemia) is characterized by a chronic hemolytic anemia and a defect in the synthesis of hemoglobin. Thalassemia minor is a subclinical anomaly detectable by laboratory examination, but is not a disease. Thalassemia major is a severe and chronic disorder which leads to early death. The inability to synthesize normal hemoglobin is genetically determined. Persons with thalassemia minor are heterozygous, patients with thalessemia major homozygous, for the dominantly inherited abnormal gene.[181] In the major form, pallor, mild icterus, and splenomegaly develop after birth although the basic anomaly is congenital. Without treatment the anemia progresses rapidly, leading to cardiac and respiratory distress and failure. Patients are kept alive by blood transfusion. Postnatal malformations of the skeleton such as thickening of the membranous bones of the face and skull and bulging of the tubular bones make their appearance. A characteristic "mongolian" facies develops.

Sickle-cell disease consists of a hemolytic anemia aggravated by crises and associated with a defect in hemoglobin synthesis. Sickling of the erythrocytes is a characteristic laboratory finding, but the sickling trait in itself does not cause disease. Persons with sicklemia may be well, if they are heterozygous for the dominantly inherited trait. Patients homozygous for the sickle trait develop sickle-cell disease. Both heterozygous and homozygous persons have the abnormal hemoglobin S, but there are marked quantitative differences. Patients with sickle-cell disease develop symptoms in the second half of the first year or later. The anemia is often overlooked, but crises cause acute disease pictures consisting of pain in the abdomen and extremities, convulsions, coma, or paralyses. In older children or adults, persistent jaundice, cholelithiasis, ulceration of the lower leg, and hypogonadism may develop. Life expectancy is reduced in the homozygous patients.[181]

Malformations of leukocytes have been described, but their role in chronic diseases has not been definitely established. The *Pelger anomaly* represents an anomaly of the nuclei of the leukocytes. The nuclear segmentation of the neutrophilic white cells is arrested. Most nuclei remain unsegmented and only seldom are there more than two segments. The nuclear chromatin shows pyknosis. The Pelger anomaly is a dominant hereditary trait, but pathologic manifestations have not been recognized in man. In rabbits the Pelger-gene has a lethal effect in the homozygous condition. Homozygous animals are characterized by severe congenital skeletal defects which resemble chondrodystrophy. Comparable changes have not yet been observed in human homozygous persons.[150] The *Alder anomaly* is characterized by coarse, deeply staining leukocytic granulations. Such leukocytes have been seen in patients with disturbed endochondral ossification.[197] The changes may be identical with those found by

Reilly[164] in patients with gargoylism. Although a genetic transmission is likely in some of the cases, the mode of inheritance has not yet been established.

Hemophilia is a well-known congenital anomaly of the blood characterized by excessive bleeding after trivial injuries. Hemorrhages from internal organs or bleeding following surgical procedures may be fatal. To prevent trauma, patients limit their activities and accept a semi-invalid way of life. A tendency to hemarthroses often cripples those patients who survive infancy and childhood. The clotting time of the blood is prolonged and the prothrombin consumption during clotting diminished. Affected persons are unable to produce antihemophilic globulin (AHG) in adequate amounts. This inability is determined by an abnormal gene which is transmitted by a sex-linked recessive mode of inheritance. As a rule, males only show the bleeder trait, but in rare instances female bleeders have been observed.[142] Such females are the product of marriage of a male bleeder to a female carrier of the recessive gene. This classical form of hemophilia, now termed hemophilia A, must be distinguished from similar, though rarer, disease pictures. Hemophilia B (PTC deficiency, Christmas factor deficiency) resembles clinically the classical type of hemophilia A, but can be distinguished from it by laboratory methods. It is due to an inherited deficiency of plasma thromboplastin component (PTC). The inability to synthesize this component is due to an abnormal sex-linked recessive gene. Owing to the fact that persons with this disorder can be effectively helped by transfusions with stored blood, their treatment is less difficult than that of patients affected by hemophilia A. Hemophilia C (PTA deficiency) is due to deficiency of a third blood factor, plasma thromboplastic antecedent. This disorder differs genetically and clinically from the types just mentioned. In general it results in a less severe bleeding tendency and hemarthroses are usually absent.[151]

Afibrinogenemia is a rare congenital defect which may lead to fatal hemorrhages at or soon after birth. Owing to the absence of fibrinogen the blood is incoagulable after many hours or days, and no fibrin deposit is produced in plasma on heating it at 56°C. for twenty minutes. This test aids in the differential diagnosis between afibrinogenemia and hemophilia, disorders which show otherwise similar clinical symptoms.[100,151] The severe form of the congenital fibrinogen defect seems to be inherited as a recessive Mendelian trait, but in cases with partial deficiency incompletely dominant inheritance may occur.[123]

Parahemophilia (Owren's disease) is due to a disturbance of the clotting mechanism which results in symptoms resembling those of hypoprothrombinemia. This bleeding tendency is referable to a deficiency of a nonprothrombin factor which normally brings about the rapid conversion of prothrombin to thrombin (Ac-globulin; labile factor). The deficiency can be acquired as a result of liver disease, scarlet fever, and other diseases. There is also a congenital form which may be due to an incompletely dominant gene.[154] The disease appears to be frequently associated with other congenital defects.[5]

Essential thrombocytopenic purpura (Werlhof's disease) is characterized clinically by petechiae, ecchymoses, and hemorrhages. The platelet count is markedly reduced, the bleeding time prolonged, and the clotting time normal. Acute and chronic forms occur and in the latter type a hereditary factor may

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play a role. The disorder has been observed repeatedly in several generations of a family.[181] It is of interest that association of thrombocytopenic purpura and hemangioma has been observed in several instances and that regression of the tumor coincided with the return of a normal number of platelets.[213] Bleeding tendencies may be due also to qualitative inferiority of the blood platelets. Glanzmann[84] and Willebrand[202] described cases of familial *thrombocytopathic purpura* characterized by petechiae, epistaxis, oral, genital and retinal hemorrhages. The bleeding time is prolonged, the coagulation time and the number of thrombocytes are normal; but morphologic changes are present in the platelets. In recent studies these findings have been confirmed and extended[115] and a dominant inheritance of the defect could be established for some of the cases.

Agammaglobulinemia was at first described by Bruton[32] in a boy who suffered from recurrent pneumococcal sepsis. The absence of gamma globulin was demonstrated by electrophoretic analysis. Since then many boys with this condition have been observed. They are affected from an early age by numerous infections of the skin, respiratory tract, and meninges. Their deficiency is due to an inborn inability to develop gamma globulin, an anomaly probably inherited as a sex-linked recessive trait. The incidence of infections can be reduced by repeated injections of gamma globulin. Congenital agammaglobulinemia can be simulated by acquired gamma globulin deficiencies which may develop at any age and in either sex.[60,176] Although congenital agammaglobulinemia is a rare disease, it is of considerable interest in this context. It is an example of a congenital anomaly which does not cause effects prenatally and which cannot be detected by external inspection or autopsy. It leads to repeated and severe infections in postnatal life, to diseases which are justly attributed to bacterial invasions. What such an inborn defect may mean to a family thus affected will be appreciated by persons who have encountered children with agammaglobulinemia. The short reports of the course of recurrent infections cannot convey the suffering of a child afflicted by this invisible congenital anomaly. Parents of affected children may be accused injustly of lack of cleanliness or lack of care. If neglect can be excluded, a "constitutional inferiority" will be blamed for the unusual susceptibility to infections. The finding of the chemical substrate for such a tendency to infections is a definite step forward in the concept of "constitutional factors," particularly since it offers a rational treatment for the defect.

METABOLIC ANOMALIES

Since the publication of the work of Garrod[82] the inborn errors of metabolism have been recognized as the classical examples of chemical hereditary anomalies. It is well-known that inborn errors of metabolism may be harmless and compatible with a long and healthy life. Other metabolic errors may become pathogenic by adverse environmental conditions or with advancing age. This statement implies that some diseases resulting from inborn errors of metabolism are not determined exclusively by genetic factors.

Many malformations are due to metabolic disturbances. Hereditary congenital malformations are probably due to inborn errors of metabolism which become manifest during early stages of intrauterine development. However,

we must not assume that all congenital malformations due to metabolic disturbance are necessarily hereditary. It has been shown in recent experimental studies that withholding of nutrients or administration of antimetabolites at certain phases of prenatal development may result in malformations indistinguishable from those produced by hereditary factors.[208] Of great interest are those malformations which, though attributable to inherited metabolic anomalies, develop before our eyes in postnatal life. Vitamin D-resistant rickets, gargoylism, and the osseous malformations in thalassemia exemplify this category. It is clear, therefore, that there can be no sharp borders between metabolic errors and malformations. Garrod[82] has pointed out that an anomaly such as albinism can be conceived of as an inborn error of metabolism or as a "malformation by arrest."

Albinism is due to an inability to convert precursor substances into melanin pigments. Whether the absence of dopa-oxidase or of tyrosinase is responsible for the anomaly is still under discussion.[126] There are various types and degrees of albinism and different modes of inheritance.[68,181] However, most of the cases are due to a recessive gene. The concept of albinism as a malformation is supported by the fact that it may be associated with polydactylism, hypertelorism, amyoplasia congenita, and others.[119]

In *alkaptonuria* the transformation of phenylalanine and tyrosine is interrupted at the stage of homogentisic acid, which is eliminated in the urine. The condition is congenital and sometimes discovered early by the blackening of urine stains on diapers. It is compatible with long life. Ochronosis, a dark pigmentation, appears later in the scleras, the gums, and in the cartilages of the nose and of the ears. More serious complications appear when the patients reach middle age. A painful stiffness of the large joints and spine with limitation of motion becomes noticeable. Deformities of the spine and a stooping posture develop. Heart disease and urinary stones are not uncommon. The intensity of the pathologic symptoms varies in different patients.[80] Ochronosis is not a harmless curiosity but may lead to disabling arthritis and ankylosing spondylitis. Calcific aortic stenosis, severe arteriosclerosis, and ochronotic nephrosis have been reported.[127] Alkaptonuria is due to a recessive Mendelian factor, but it seems to occur more often in males than in females. In rare instances dominant transmission has occurred.[181] It is of interest that ochronosis may develop as an acquired, nonhereditary condition after prolonged administration of phenol-containing compounds to wounds or ulcers.[127] *Phenylketonuria*, an inability to transform phenylalanine into tyrosine, has been discussed above (p. 51).

Cystinuria is a congenital anomaly characterized by excretion of flat, hexagonal cystine crystals in the urine. In adults quantities as large as 1 gram may be eliminated in twenty-four hours. In addition, lysine and arginine are often found in the urine of patients with cystinuria. Dent and Rose[53] established that the plasma of such persons contained normal concentration of all the detectable amino acids and concluded that the cause of the excessive excretion of the amino acids is a low renal threshold and not an error of amino acid metabolism. A similar renal permeability is often present in some of the patient's relatives. This condition, which is not rare, may result in the formation of stones composed of cystine. It is not certain that cystinuria is in any way related to cystinosis.

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Cystinosis is a serious and rare disease, usually seen in children and characterized by cystine deposits in the liver, spleen, lymph nodes, bone marrow, and other organs. Affected children show retarded growth, rickets, glycosuria, albuminuria, and amino-aciduria. This disease, known as the Lignac-de Toni-Fanconi syndrome, has a long and complicated history and there are still many features which need further elucidation. Although many amino acids are excreted in excessive amounts, cystine may not be among them. At the same time cystine crystals can be detected in the cornea by the slit-lamp, in bone marrow by puncture, or in lymph nodes by biopsy. This severe and protracted disease may be found in several children of the same family and recessive inheritance is probably the rule. However, cystinuria has been observed occasionally in a parent of a child with cystinosis. Good reviews of this complicated subject are available.[21,59,79]

Hepatolenticular degeneration (Wilson's disease) is an extrapyramidal disorder which shows clinical manifestations in the second or third decade and ends fatally within a few months or years. Tremor, dysphagia, impairment of speech, and muscular hypertonia develop. The neurological changes are accompanied by a cirrhotic process of the liver and in many cases a ring of greenish pigment (Kayser-Fleischer) can be observed near the limbus of the cornea. The lenticular nucleus shows destruction of ganglion cells and gliosis. Sporadic cases are rare. Several children of a family are often affected, and a recessive mode of inheritance has been assumed. It has been established[199] that affected persons have a persistent amino-aciduria which differs from amino-aciduria of other types of liver cirrhosis, since the plasma amino acid level is not elevated. There is often a high urinary excretion of copper, which is associated with low values of serum copper and coeruloplasmin (copper enzyme).[15] Wilson's disease is not a congenital disease, but it is likely that the underlying metabolic disorder is. This belief is based upon the fact that a high fetal and infant mortality has been observed in affected families.[181] In addition, amino-aciduria has been established in young asymptomatic siblings of affected persons.[199]

Glycogen storage disease is a disorder of carbohydrate metabolism resulting in storage of excessive quantities of glycogen in the liver, kidneys, heart, and other organs. In hepatic glycogen disease (von Gierke's disease) the formation of glucose from glycogen is disturbed due to absence of glucose-6-phosphatase.[43] Hepatomegaly, retardation of growth, vomiting, convulsions, and obesity are clinical manifestations. Such children require much attention because of their hypoglycemic attacks, but they may outgrow their disease. Laboratory tests show hypoglycemia in the fasting state, hyperglycemia after ingestion of glucose, lipemia, and ketonuria. It is usually stated that this condition is inherited as a recessive trait, but in some families incomplete dominance must be considered. It is probable that more than one type of this disorder exists. Cardiac glycogen disease differs from the hepatic form chemically as well as clinically. Symptoms appear soon after birth and death occurs within a few months.

Galactosemia is a disorder of carbohydrate metabolism which results in failure to gain weight, lethargy, mental deficiency, hepatomegaly, cataracts, and galactosuria. In such patients ingested galactose is not converted to glu-

cose and administration of galactose reduces the dextrose level of the blood.[138] The disease is probably inherited as a recessive character, but reduced tolerance for galactose has been demonstrated in the parent of a patient.[105] This disease can be greatly ameliorated by withholding milk and lactose from the diet.

In *familial hyperlipemia* the neutral fat fraction of the blood is markedly increased and the serum assumes a milky appearance. Hepatosplenomegaly, xanthomatous nodules of the skin, and lipemia retinalis can be observed. The patients suffer from recurrent attacks of abdominal pain and vomiting suggestive of an acute abdominal disorder. The symptoms can be improved by a low fat diet.[104]

Congenital porphyria occurs in persons who are unable to metabolize properly uroporphyrine I, which accumulates in excessive amounts in many tissues. A red-colored urine may be noticed at birth and the bones and teeth become discolored by a purplish-brown impregnation with the porphyrin. The presence of porphyrin in the skin and ocular tissues is responsible for the sensitivity to sunlight. After exposure to sunlight, pruritus, erythemia, and vesiculobullous eruptions develop on the skin (hydroa estivale). These lesions result in crusts and pigmented scars. Severe disfigurement may occur with loss of substance of the ears, nose, and fingers. Ocular complications include conjunctivitis, iritis, and ulcerative keratitis. Porphyria has been found in patients with epidermolysis bullosa, xeroderma pigmentosum, and other diseases of the skin.[58,151] The condition may be associated with congenital malformations such as oxycephaly, syndactyly, aplasia of the mammary glands or of the gall bladder and with hypoplastic or cystic kidneys. Congenital porphyria is usually a recessive condition with a high frequency of consanguinity in the affected families.[181]

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DISCUSSION AND SUMMARY

In the foregoing pages many congenital anomalies were enumerated which play a role in the etiology of chronic diseases. Only a limited number could be mentioned to exemplify certain characteristic features of this area of human pathology. The anomalies cited have only one point in common: they have their roots in prenatal life. In a longitudinal study of chronic diseases, early pathogenic factors must be considered and emphasized. This approach, however, should not convey the idea that postnatal factors cannot modify prenatal injuries. Although some congenital malformations and diseases interfere with health from birth on, others can be well tolerated until secondary factors cause disease. In such cases the anomaly represents a point of reduced resistance which becomes diseased by secondary factors such as infection, trauma, and others, factors which usually are not pathogenic for normal tissues. The interval between birth and onset of disease may be short or long. Secondary pathogenic factors may be well recognized or concealed. In the presence of congenital anomalies, disease may often be prevented or cured by elimination of secondary factors.

The knowledge of prenatal disease factors, however, is of great practical and theoretical importance. Many examples were cited in the preceding pages which show that it may be dangerous to mistake complications of congenital

malformations for the disease proper. This is particularly true for certain malformations of the urinary tract which, if recognized in time, can be cured by surgical measures, but lead to a hopeless state if left to palliative treatment. Some congenital malformations of the intestinal tract may lead to chronic illness, if treated by dietary measures or psychotherapy only, while surgical removal of the abnormal viscus is required for a cure. Examples were cited of malformations of the respiratory tract, which may receive improper treatment unless their teratologic nature is recognized.

Knowledge of some of the peculiarities of congenital defects may assist in the diagnosis of many disorders. Congenital malformations are often multiple since prenatal factors interfering with embryonic development often injure many tissues and organs. To the observing clinician, the combination of congenital anomalies are of great interest and there is a tendency to correlate them and to group them into syndromes. Such syndromes, though often variable and ill-defined, are of definite value. A harmless skin lesion or a minor skeletal defect may, if correctly interpreted, aid in the rapid recognition of an internal disease. Melanin spots of the lips and oral mucosa combined with intestinal symptoms may direct the alert clinician to a diagnosis of intestinal polyposis. Obesity in a young child is a puzzling condition which requires a complicated differential diagnosis. The finding of polydactylism in such a child permits a fairly safe classification of the case and foreshadows a grave prognosis (p. 79). A convulsion of a child with nevus flammeus on the face is indicative of meningeal angioma. Every pediatrician has at times the painful duty to predict mental deficiency of a newborn child, because of slightly abnormal, mongoloid features. It is a matter of course that the association of external features and internal disorders is not immutable. It is in exceptional cases only that a diagnosis can be made by observation of a single sign, but sometimes the finding of an external anomaly belonging to a syndrome can rapidly clarify a puzzling internal disease.

Microscopic malformations help to explain sometimes complicated disease pictures in persons who appear well formed at birth. Congenital absence of parasympathetic ganglion cells in the plexus of the rectosigmoid explains the extremely obstinate constipation, emaciation, and external deformation of children with megacolon. Malformations of the blood such as spherocytosis, thalassemia, or sickling lead to disturbances of many organs; anemia, jaundice, and skeletal or cutaneous changes may be outward manifestations. Congenital abnormalities of the cells of the pancreatic acini and of the mucous glands in the respiratory tract cause a multitude of pathologic manifestations and protracted illness, labeled "cystic fibrosis of the pancreas."[108] It is thought that an enzymatic, cellular defect may be at the root of the pluriglandular anomaly. Such chemical disabilities which are probably the basis of most congenital defects may exert their adverse influence before and after birth. It may be found eventually that prenatal chemical disturbances are responsible for most congenital malformations, but it should be remembered that physical forces also may be injurious to the embryo and fetus. In some disease pictures, congenital chemical anomalies begin their destructive action after birth. This is true in congenital

porphyria but also in such skeletal malformations as gargoylism or Morquio's disease which are hardly detectable at birth yet produce serious deformities during childhood. Congenital alkaptonuria leads to deforming skeletal anomalies when the patients reach middle age.

The majority of the congenital malformations cited above have a genetic background and heredity can be demonstrated in many instances. It should be emphasized, however, that nongenetic factors can also cause congenital malformations and congenital syndromes. It has been pointed out before that hereditary malformations and their phenocopies may show close clinical resemblance. Even syndromes of multiple congenital anomalies may be of environmental origin. Endemic cretinism is a case in point. This disorder combines congenital defects of the thyroid, the brain, and the ear with many secondary anomalies developing in postnatal life. Its pleomorphism and protracted course can be compared to those of Marfan's syndrome or of the Laurence-Moon-Biedl syndrome, which, however, are genetically determined. Endemic cretinism affects often several members of a family but it is due to maternal dietary factors and not to heredity.[65] It has been mentioned that a syndrome of congenital malformations and defects appears in children of mothers who had rubella in early pregnancy (p. 47) and there is no proof that heredity plays a role in the etiology of the Sturge-Weber and McCune-Albright syndromes (pp. 75 and 80). It is not justified, therefore, to assume that all syndromes of multiple anomalies and malformations are genetically determined. In the foregoing review, hereditary and nonhereditary congenital anomalies were included. To the bearer of such anomalies this point of differentiation is usually irrelevant, but it is of importance to his family and to the community. Genetic and ecologic research methods differ and preventive recommendations are dissimilar. The role of genetic factors in chronic diseases of later life has been discussed in a previous number of this JOURNAL.[85,227] The existence of nongenetic factors and of phenocopies produced by them had to be stressed in the present article.

It is clear that children and adults who survive birth in spite of their congenital anomalies must receive the best care, schooling, and treatment available to make them as normal and as useful to society as possible. If they cannot be adjusted physically or mentally to the free and normal environment of their families and communities, they must be given the opportunity to live in institutions which can deal best with their handicaps. Treatment will be left, as in the past, to specialists who are best suited to repair or alleviate damage done in prenatal life. In recent years brilliant results have been obtained by surgical measures in the repair of congenital malformations. Many children born with congenital malformations of the heart, intestine, urinary organs, and others can be restored to health by surgical procedures. However, other malformations are not suitable for such measures and incapacitate their bearers. Some severe defects considered lethal in the past are now made compatible with life by surgical or medical care without complete restoration to health. Palliative measures are particularly disappointing in patients with multiple anomalies who develop successively diseases in different organs. Patients with mental deficiency present a special problem. Although education and care can improve their lot, medical

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treatment is unsuccessful in most cases. It is clear that in the field of congenital anomalies, prevention and not repair must be the aim for the future.

Rational preventive measures require knowledge of the causes of congenital anomalies which are still obscure in most instances. Etiological research along these lines can be carried on in many ways. Physicians can make important contributions by observations of patients, by recording their histories and the histories of their families. In this way disease processes can be studied longitudinally by any physician, particularly by general practitioners. However, clinical studies are frequently made by specialists who are greatly interested in the causation of disorders of certain organs with which they are frequently confronted. They are well suited for such investigations because of the wealth of material available to them and because of their ability to classify and diagnose rarer disorders of their specialty. Yet, in etiologic research of congenital anomalies, observations should never be limited to the organ system of a single specialty but should be extended to the patient as a whole, to all his pathologic manifestations, and to the entire course of the disease process. As emphasized in the preceding pages, adverse prenatal factors have a marked tendency to involve many parts of the body, thus leading to multiple pathologic manifestations. Specialization which proves so useful in the treatment of diseases may be less effective in the search for prenatal disease factors. A broad approach should be considered particularly by those responsible for the planning and organization of etiologic research in the field of congenital anomalies. Such research should not be organized strictly along the lines of the established medical specialities. Etiologically a congenital cardiac defect may be closer related to a congenital defect of the eye than to heart disease of old age. It should be remembered in this connection that a fundamental contribution to our knowledge of the etiology of congenital heart disease was made by an ophthalmologist.[90] Urinalyses have revealed the causes of some forms of mental deficiency. One can seldom predict from which quarter the solution of a medical problem will come, and this is true particularly for congenital problems, since in prenatal life the boundaries of specialties do not exist.

The recognition of congenital anomalies and malformations as a major cause of diseases has aroused a new interest in the origins of prenatal errors of development. Geneticists, embryologists, nutritionists, and many clinical investigators have been stimulated to direct their attention to congenital disorders. A great deal of work concerned with experimental production of congenital malformations had been done in the past in lower classes of animals. In recent years such experiments have been extended successfully to mammals. Teratology, the science of congenital malformations, is an old science. Although dormant in the early decades of this century, it is undergoing a rennaissance at the present time. Teratology is no longer limited to congenital monstrosities, but deals also with minor defects resulting in diseases and functional disturbances. Much remains to be done to collect, to sift, and to coordinate the wealth of knowledge available in this field. It is to be hoped that this review will contribute to the recognition of this branch of medical research and to promotion of investigations concerned with prenatal life.

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Editorials

SOME COMMENTS ON THE MEDICAL MANAGEMENT OF THE OLDER PERSON

Informal discussions with seasoned clinicians concerning the care of the older patient cast doubt on the advisability of establishing geriatrics as an independent discipline. This opinion does not invalidate the belief that the medical problems of the aged are often managed differently than are the same problems in younger individuals. But the principles of management are usually the same for all ages, with the proviso that each sick person is a problem unto himself and must be treated accordingly.

The disorders sometimes listed under the category of geriatrics are being vigorously investigated in the modern university hospital and research institute. Studies of the biology, and thus the aging, of the individual cell and such multiple cell organisms as *Homo sapiens* are being conducted in most colleges and medical schools. No useful purpose would be served by dissociating these innumerable researches from the disciplines of biology and medicine into the proposed subspecialty of geriatrics.

Long-term medical care of the aged in the home is often difficult to arrange to the satisfaction of the patient and the family. Institutional care of the aged sick is largely provided by tax supported hospitals for the chronically ill. These services are often inadequate; but the trend is toward improvement in many areas, particularly where an affiliation has been established between the hospital and a university. Opportunities should be developed to further knowledge concerning the impact of present and changing socioeconomic and sociopsychologic forces upon the older individual and those members of the family unit who are perforce affected by the presence and pressures of the patient.

It would appear that the needs for the physician's training in geriatrics can best be met by strengthening the university's facilities in the basic sciences and the established clinical divisions. Many opportunities for demonstrating the special medical needs of the older person are available in institutions for long-term illness, since the majority of disabilities associated with chronic diseases occur in middle and late life.

An expected difficulty encountered during instruction of medical students in the management of the aged patient is the retarded interest of the student in the slow changes observed in this sick group compared with the spectacular therapeutic responses often seen in younger patients with dramatic, acute disorders. It is only when the student comes to appreciate that the bulk of his future practice will consist of individuals, often aged, who harbor slowly progressive morbid processes, that he is awakened to the need of enlarging his horizon as a human being and as a physician.

The satisfactory management of the older patient depends upon the presence of the experienced and empathic physician. The writer has drawn heavily upon the opinions of such individuals for the notions now to be presented.

Although the physician is usually depicted as a healer, his office might be cast in a more positive light with respect to the management of the elderly, if his goal was set at assisting the patient to achieve the greatest degree of happiness under the special circumstances. I remember a ward walk on a visit to Baltimore some years back. In the course of the morning, Dr. Longcope had occasion to remark that each patient ought to feel somewhat the better for the physician's visit. This was a responsibility of the doctor, else what useful purpose would be served by frequent calls in the many instances in which specific therapeutic measures were not available. This attitude is essential in the care of the aged. Its performance is more easily accomplished by accepting the principle that "the physician should treat each patient the way he would wish to be treated if he were that patient in that bed at that time."

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Dana W. Atchley, in his teaching, points out that the principles of medical management are essentially the same for individuals of all ages albeit the *same* medical problem is handled *differently* in *different* patients. He uses this telling analogy: the principles of driving an automobile are uniform, but one drives differently on the New Jersey Turnpike than on a narrow, winding road in the Rocky Mountains.

Atchley has suggested that the total medical needs of the older patient may be better served if the thought expressed in the word

appraisal be substituted for *diagnosis*,
and the word
management be substituted for *treatment or cure*.

Such an attitude would assist the physician to shift his preoccupation with cure to a fascination for management of the sick individual. This is particularly important in the care of the older patient where the impact of living adds its weight to the burden of disease. The elderly patient may be "cured" of his "fever" but a comprehensive history and inventory may disclose personal problems more damaging than the "fever."

The modern school of "restorative medicine," led by Rusk and his associates, has recreated and extended fundamentals of management of the sick which are applicable to the older patient. There can be little disagreement with the belief that the physician has performed a useful service when he assists the sick patient to achieve his fullest physical and social potential. This may mean such limited progressive actions as these: to sit instead of being bedfast; to stand instead of being confined to a chair; or to walk when this has not been possible earlier. A fair generalization for the elderly patient is this: he should be permitted to be as active as he wishes without injuring himself.

The older individual in the United States does not usually enjoy the familial station and privileges accorded the oldster in the China of the recent past. He may possess a Social Security card but he has relinquished his seat in the subway and the authority which commands the obedience of his children. The elderly

American of today is often preoccupied with his good recollections and his bad memory. He may become a nuisance to his young associates because of his irascibility, his mutterings about loose dentures, or the glee with which he describes the easy delivery of a delayed stool. W. B. Cannon has called attention to the extraordinary interest of the elderly in such simple physiologic activities. Although the layman is apt to have limited tolerance for the soliloquies and complaints of the older patient, the physician does not have this privilege.

The principle of minimal interference is paramount in the management of the elderly. The older a patient, the less his way of life should be disturbed. Destruction of an established pattern of life may result in confusion and tragedy. The young amorphous personality can usually be vigorously molded without danger. In contrast, the older, more rigid personality is like a crystal, easily shattered by unwise impacts.

There is no specific remedy for aging. G. R. Cameron holds the view that aging represents "the vector sum of a number of morbid processes most of which take a time to develop, and often a long time to reach a serious climax." Cameron and others believe that many of these pathologic states begin in early life. Hope lies in learning more about the beginnings of these disorders, their causes and mechanisms. It may not be facetious to remark that the proper approach to geriatrics is through pediatrics. Charles Minot hypothesized that senescence begins at birth. Montaigne put it this way, "Death is but an end to dying."

But, fortunately, man has an elusive way of procrastinating with death if not with dying. The physician's role in managing the elderly patient may be expressed in the following general terms:

a. The practices of good medicine are to be made available to him, irrespective of whether the disorder is acute and flagrant, or chronic and indolent.

b. The crystallized life pattern of the elderly patient makes serious interference perilous.

c. The goal of the physician is to assist the older patient to reach the highest physical and social potential, irrespective of the nature of the illness.

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THE LONG FOLLOW-UP

It is generally agreed that a vital part of the study of chronic disease is the long follow-up. Despite this obvious fact, the long follow-up is one of the most neglected of our research tools. There are several reasons for this which need more adequate attention than they have received.

Commonly in the past, and not rarely even now, quite wrong or at least incomplete conclusions have resulted from the short-term study of patients over periods of weeks or months or even a few years, no matter how elaborate the so-called vertical investigation. Invaluable as much of the immediate or short-term study of disease has proved to be, many questions can be answered only by the long follow-up. For example, when coronary thrombosis first began to be commonly diagnosed in the mid-twenties, it was generally believed, and so stated, that three years of survival after an attack might be possible with the best of good fortune. With each decade since, there has developed an increasing optimism about the prognosis of this disease, resulting simply from observation of many patients who survived the original attack to live active lives for a long time. An example of this is a patient of mine, whom I saw in consultation during an absolutely typical illness with acute myocardial infarction, in 1927, at the age of 51 years. He is perfectly well today, 28 years later, despite a fair-sized scar in his heart which does not prevent him from playing 18 holes of golf, free of symptoms, at the age of 79. Of course, he is one of the long survivors, but the point of view in 1927 was such that, had he been seen then at the age of 79, the correct diagnosis would have been ruled out because he had survived for so long and in such good health. At the present time, the average survival period after acute coronary thrombosis is not far from ten years; this figure includes of course the data from both mild and severe cases. This example is one of the more impressive results of the long follow-up.

An important reason why the long follow-up has been so often neglected in the past is that many of the professors of medicine in the medical schools of the country and many of the clinical researchers are more or less peripatetic, progressing from one post and city to another as positions of academically higher importance present themselves. Since these are the individuals who do most of the medical writing, the studies which they report are, for the most part, of relatively acute conditions or, at best, over a few years only, so far as their own observations go, and in impersonal public clinics. The practicing physicians who follow many private patients, often very carefully, for many years in one locality are for the most part silent. It would be a great service to medical progress if the more carefully and better trained practicing physicians could present the more valuable long follow-up studies of their personal patients. We should all make a more concerted effort to bring this to pass. As everyone

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knows, it is much easier and more productive to follow private patients, no matter what their social and economic status, than to follow so-called public patients in the clinics, although there are, of course, exceptions.

It is of importance, when needed, to have expert advice from a biostatistician, and in planning a complicated follow-up study such advice may wisely be requested at the beginning. However, it is to be emphasized that a relatively few cases studied well with accurate diagnoses and good follow-up have a much greater value than thousands of poorly diagnosed or inadequately studied cases, despite the superficial impression that statistically the latter sound better.

It is not an easy or simple matter to conduct a follow-up study of many patients over periods of many years in a satisfactory manner. Too often, councils, committees, and individuals responsible for the material or moral support of research have indiscriminately rejected applications for funds for follow-up studies on the basis that they are a part of the routine care of patients. Sometimes this is true or in part true, but often it is not. A much more careful appraisal of each application should be made than has been the custom in the past. Questions should be asked in each case concerning several points: first, the need of the follow-up, which of course varies greatly from case to case; second, the ability, in this regard, of the investigators; third, its magnitude and, hence, its expense, also of wide variety; and fourth, the possibility or indeed, not rarely, the probability that it cannot be done without outside support.

Finally, a word or two may be helpfully added as to the technique of the long follow-up. It is well to introduce the idea to the patient on the occasion of first meeting him, even though, at the moment, there is no serious disease to be treated. The intervals between re-examinations may be long, even up to five years, although I have found that annual checkups are the most satisfactory in maintaining contact with patients for the long follow-up. If one acts as a consultant, he should be very conscientious in sending, after each examination, a full report to the family physician, with copies, as circumstance may dictate, to the patient himself. If, for one reason or another, intervals of years elapse and the patient moves away or dies, there are various methods that may be used to trace him. The family doctor or some relative may have the needed information. If not, one may have to resort to the departments of vital statistics in the state and city or town where the patient once resided. One may enter a note of inquiry in the local newspapers, or even in the journals of a larger city whither the patient or some relative or friend may have moved. My colleagues and I have had some success by that procedure. Another method which has been fruitful is to search for the patient or some possible relative of the same name in the current annual telephone directory of the original city or town of residence, or in neighboring towns, or the nearest larger cities. Not infrequently the patient or his family may have moved to a nearby street or some other suburb of the same city. When letters fail, a telephone call or a personal visit may succeed.

In summary, then, we may hope that the value of the long follow-up in medical research will be more widely recognized, effected, and supported, particularly in establishing a base line of the natural history of various diseases for

comparison with the effect of the many new medical and surgicial therapeutic and preventive measures that are being constantly introduced. We can better judge the effect of treatment and prevention in coronary heart disease if we recognize, as is possible even now, the extraordinarily varied natural course of the disease through decades of time. We can better appraise the result of sympathectomy and the various hypotensive drugs if we know how hypertensive patients do without such treatment; and we can determine the ultimate effect of mitral valve surgery, which promises so much benefit to us now, if we have adequate knowledge of the course of pure mitral stenosis before its surgical treatment became a practical routine.

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PROGNOSIS IN BRONCHIAL ASTHMA

The medical student or intern has usually obtained his initial impressions of the problems of bronchial asthma by the study and care of patients hospitalized for this condition. Once he is in general practice, he quickly realizes that he must radically revise his ideas as to the characteristics of this ailment. He discovers that the majority of patients with bronchial asthma, as seen in his practice, remain ambulatory and rarely, if ever, require the services of a hospital. Their asthmatic attacks usually are mild, paroxysmal, and readily controlled by self medication; rarely are they overwhelming, provided the patient is temperate in his food and drink, and gives proper respect to threat of acute upper respiratory infections, fatigue, and emotional excesses. He may seldom require the physician's services in office or home. There are, however, hospitalized cases which represent the more complicated, irreversible, intractable, and advanced form of asthma, which is often marked by a depletion of vitality and waning recuperative powers.

An accurate study of this clinical condition requires, as an initial step, careful classification of the various types of bronchial asthma, and separation of the cases upon an etiologic basis. The means at our disposal include: comprehensive history; thorough physical examination; x-rays of the chest and of the sinuses; skin tests with extracts of the important air-borne excitants, such as pollens, dusts, animal danders, and of the important foods; and trial and error procedures with the excitants suspected as eliciting agents. Whether the patient's symptoms are due to foods, air-borne excitants (inhalants), or infective agents, or any combination of them, can usually be determined successfully.

In the first two decades of life, specific food sensitization is often found to be the cause of bronchial asthma. Such food cases rarely appear in any statistical study of hospitalized asthmatic patients, since their attacks are usually self-limited and moderate in degree. When they are severe and prostrating, they are usually abrupt and temporary, and leave no apparent physical damage requiring treatment or convalescence in the hospital. Even the exquisitely sensitive food cases, fortunately rare, are seldom found in the hospital lists since the ingestion of the food excitant, such as egg, nut, or fish, is followed swiftly by death before admission to the hospital can be arranged.

In addition to the food-sensitive group, there are asthmatic patients, usually in the first four decades of life, whose attacks are caused by air-borne substances present in the inspired air, such as pollens, dusts, or animal danders. A change of residence, or the disposal of household pets may cause the asthma to disappear, leaving no pathologic trace or complicating feature in its wake. Such cases may never appear in the medical records of either office or hospital.

It is the asthmatic patient of any age, unable to cope with respiratory infection, acute or chronic, who is most likely to become a hospital statistic. Because of emotional or physical excesses, debilitating illnesses, or neglect of health,

such persons may suddenly be in critical need of hospitalization. The asthmatic symptoms, usually under partial control, become increasingly difficult to manage, being aggravated often by associated or secondary pathologic conditions, such as paranasal sinusitis, bronchitis, myocardial disease, or pneumonia. The outstanding feature of this third group, so closely linked with infection, is the severity, chronicity, and, frequently, the intractability of the symptoms, which require hospitalization far more often than is true with cases of asthma due to foods or inhaled substances.

Hospital statistics on the prognosis of bronchial asthma, therefore, are difficult to evaluate accurately. Far more dependable information would be obtained from the study of cases attending the large outpatient departments of hospitals, and cases in private practices devoted to the treatment of all varities of bronchial asthma.

In this issue, Westlund and Hougen[1] have presented an excellent study of statistical data assembled from the Oslo City Hospital, and have shown, satisfactorily, the prognosis in the cases of bronchial asthma which were hospitalized. The authors well recognize the limitations present in any such study when they state that, "Only an unknown percentage of all the cases of bronchial asthma is admitted to the hospital." It is the conviction of many physicians that, while the percentage of hospitalized cases of bronchial asthma is unknown, it is relatively small, and growing rapidly smaller with the physician's home use of the antibiotics and the steroid hormones. These therapeutic agents are notably effective in the treatment of the third, or infective group of asthmatics which furnishes the great majority of the hospitalized patients. The authors take pains to point out that the data they have assembled may not be quite pertinent to any but hospitalized cases when they write, "The prognosis for those patients who are never hospitalized, may be quite different, even better." It is the belief of many physicians that the prognosis for the large group of unhospitalized patients is decidedly better, since their symptoms are milder and their causative factors more readily identified and removed.

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Book Reviews

HOW TO FREE YOURSELF FROM NERVOUS TENSION. By Samuel W. Gutwirth, M.D. Indexed. 200 Pages. 57 Figures. Chicago, Illinois, 1955. Regnery. Price $3.95.

This volume is devoted to an exposition of "progressive relaxation", which was first elaborated by Dr. Edmund Jacobson. Dr. Gutwirth suggests that people may learn to practice progressive relaxation through reading of the book. The first half of the text is a detailed exposition, with illustrations, of the technique and practice by which progressive relaxation is achieved. The latter half of the volume is a question and answer section. This part is an even admixture of specific advice, enthusiastic claims, and a good deal of misinformation about various illnesses.

The do-it-yourself tradition is not new to either psychiatry or medicine. Dr. Gutwirth is clearly enthusiastic about helping people who, he feels, cannot get help from other sources. In his dedication of the book to Dr. Jacobson, Dr. Gutwirth states that the former inspired him, " . . . to 'carry the gospel' to the multitudes." The claims made for beneficial effects of progressive relaxation, however, are not substantiated by any evidence.

Eugene Meyer

HEART DISEASE. By Geoffrey Bourne, M.D. Pp. 135, with 4 figures; indexed. Chicago, 1955, Henry Regnery Company. Price $2.25.

TUBERCULOSIS. By Cedric Shaw, M.D. Pp. 160, with 16 figures. Chicago, 1955, Henry Regnery Company. Price $2.25.

VARICOSE VEINS. By R. Rowden Foote, M.D. Pp. 110, with 16 figures; indexed. Chicago, 1955, Henry Regnery Company. Price $2.25.

SKIN DISEASES. By Reginald T. Brain, M.D. Pp. 158, with 3 figures; indexed. Chicago, 1955, Henry Regnery Company. Price $2.25.

These four small volumes are the first of a series prepared by a group of British physicians under the distinguished editorship of Lord Horder. The general purpose of the series is summed up in "a note by the Editor," as follows:

"It is natural and reasonable for a patient to be interested in the disease from which he suffers. Under modern conditions this natural curiosity is too often satisfied in a catch-penny manner, incomplete and misleading where it is not actively harmful; so that doctors often find themselves having to waste precious time in disabusing patients of false beliefs about their ailments.

"It is the object of this series of books to give precise, authoritative information; to take the patient into the doctor's confidence so that both work together to get the patient better; to explain things simply and intelligibly; to offer sufferers whatever hope the most up-to-date medical knowledge can honestly offer; in short to tell the truth about diseases as it has never been told to the general public in print before.

"The series is designed to give general background information only. The books are not courses of self-treatment; nor will the writers reply to any queries addressed to them by the general public. Consult your own doctor about your own case."

The books are all short, from 100 to 160 pages in length, and in general seem extremely well done. The critical comment might be made that in some of them there is a good deal of technical detail which would seem relatively undesirable for the uninitiated layman.

There are bound to be differences of opinion as to the desirability of advising patients to conduct extensive reading concerning the diseases from which they, or members of their family, suffer. It is, by and large, sound advice that the patient should obtain information concerning his own case from his own physician who is able to interpret the situation as it affects the patient, not as it affects ten thousand sufferers from the same condition. When the patient reads, he is often unable to interpret medical literature (even couched in simple terms) *as it applies to him;* and the circumstance not infrequently arises that his legitimate symptoms are augmented by others of iatrogenic origin.

By and large, however, one cannot keep patients from reading; and if they must read, this series of books may, in some instances at least, be helpful.

Before the physician advises his patient to purchase a book for the layman on "Heart Disease," however, he would do well to read the book himself and to measure the impact of its contents on what he knows of his own patient's psyche.

Other volumes of this series are to be published.

J. E. Moore

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